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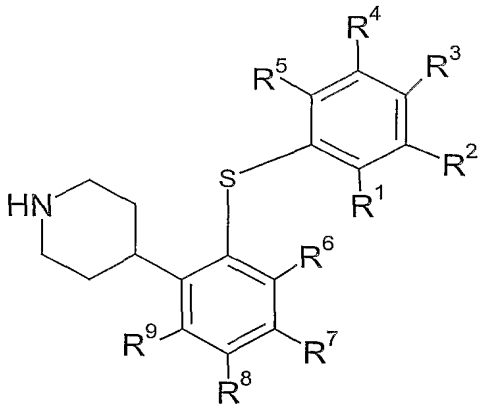
(54) Title: 4-(2-PHENYLSULFANYL-PHENYL)-PIPERIDINE DERIVATIVES AS SEROTONIN REUPTAKE INHIBITORS



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(57) Abstract: The invention provides compounds represented by the general formula (I) wherein the substituents are defined in the application. The compounds are useful in the treatment of an affective disorder, including depression, anxiety disorders including general anxiety disorder and panic disorder and obsessive compulsive disorder.

4-(2-Phenylsulfanyl-phenyl)-piperidine derivatives as serotonin reuptake inhibitors

The present invention relates to novel compounds which are serotonin reuptake inhibitors and as such effective in the treatment of for example depression and anxiety.

Background of the invention

Selective serotonin reuptake inhibitors (hereinafter referred to as SSRIs) have become first choice therapeutics in the treatment of depression, certain forms of anxiety and social phobias, because they are effective, well tolerated and have a favourable safety profile compared to the classic tricyclic antidepressants.

However, clinical studies on depression indicate that non-response to SSRIs is substantial, up to 30%. Another, often neglected, factor in antidepressant treatment is compliance, which has a rather profound effect on the patient's motivation to continue pharmacotherapy.

First of all, there is the delay in therapeutic effect of SSRIs. Sometimes symptoms even worsen during the first weeks of treatment. Secondly, sexual dysfunction is a side effect common to all SSRIs. Without addressing these problems, real progress in the pharmacotherapy of depression and anxiety disorders is not likely to happen.

In order to cope with non-response, psychiatrists sometimes make use of augmentation strategies. Augmentation of antidepressant therapy may be accomplished through the co-administration of mood stabilizers such as lithium carbonate or triiodothyronin or by the use of electroshock.

The effect of combined administration of a compound that inhibits serotonin reuptake and a 5-HT_{1A} receptor antagonist has been evaluated in several studies (Innis *et al. Eur. J. Pharmacol.* **1987**, *143*, 1095-204 and Gartside *Br. J. Pharmacol.* **1995**, *115*, 1064-1070, Blier *et al. Trends in Pharmacol. Science* **1994**, *15*, 220). In these

studies, it was found that 5-HT_{1A} receptor antagonists would abolish the initial brake on 5-HT neurotransmission induced by the serotonin reuptake inhibitors and thus produce an immediate boost of 5-HT transmission and a rapid onset of therapeutic action.

Several patent applications have been filed, which cover the use of a combination of a 5-HT_{1A} antagonist and a serotonin reuptake inhibitor for the treatment of depression (see e.g. EP-A2-687472 and EP-A2-714663).

Another approach to increase terminal 5-HT would be through blockade of the 5-HT_{1B} autoreceptor. Microdialysis experiments in rats have indeed shown that increase of hippocampal 5-HT by citalopram is potentiated by GMC 2-29, an experimental 5-HT_{1B} receptor antagonist.

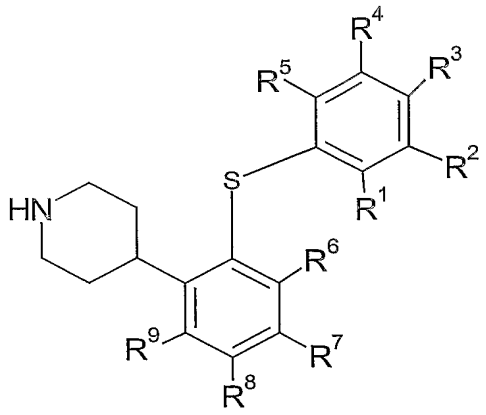
Several patent applications covering the combination of an SSRI and a 5-HT_{1B} antagonist or partial agonist have also been filed (WO 97/28141, WO 96/03400, EP-A-701819 and WO 99/13877).

It has previously been found that the combination of a serotonin reuptake inhibitor with a compound having 5-HT_{2C} antagonistic or inverse agonistic effect (compounds having a negative efficacy at the 5-HT_{2C} receptor) provides a considerable increase in the level of 5-HT in terminal areas, as measured in microdialysis experiments (WO 01/41701). This would imply a shorter onset of antidepressant effect in the clinic and an augmentation or potentiation of the therapeutic effect of the serotonin reuptake inhibitor (SRI).

The present invention provides compounds which are serotonin reuptake inhibitors for the treatment of affective disorders, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia. Some of the compounds also have a combined effect of serotonin reuptake inhibition and 5-HT_{2C} receptor modulation, which according to WO01/41701 would imply a faster onset of antidepressant activity.

Summary of the invention

The present invention provides compounds of the general formula I



(I)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are as defined below.

The invention provides a compound according to the above for use as a medicament.

The invention provides a pharmaceutical composition comprising a compound according to the above or a pharmaceutically acceptable acid addition salt thereof and at least one pharmaceutically acceptable carrier or diluent.

The invention provides the use of a compound according to the above or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of affective disorders, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia.

The invention provides a method for the treatment of an affective disorders, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia in a living animal body, including a human, comprising administering a therapeutically effective amount of a

compound according to the above or a pharmaceutically acceptable acid addition salt thereof.

Definition of substituents

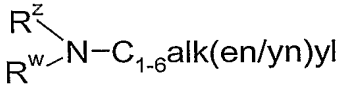
Halogen means fluoro, chloro, bromo or iodo.

The expression C_{1-6}-alk(en/yn)yl means a C_{1-6}-alkyl, C_{2-6}-alkenyl or a C_{2-6}-alkynyl group.

The term C_{1-6} alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

Similarly, C_{2-6} alkenyl and C_{2-6} alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and one triple bond respectively, including but not limited to ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

The terms C_{1-6}-alk(en/yn)yloxy, C_{1-6} alk(en/yn)ylsulfanyl, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, NR^zR^w-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl and halo-C_{1-6}-alk(en/yn)yloxy designate such groups in which the C_{1-6}-alk(en/yn)yl are as defined above. Halo means halogen.
NR^zR^w-C_{1-6}-alk(en/yn)yl designate the group



The term C_{3-8} cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, etc.

The term C_{3-8} cycloalkenyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms and including one double bond.

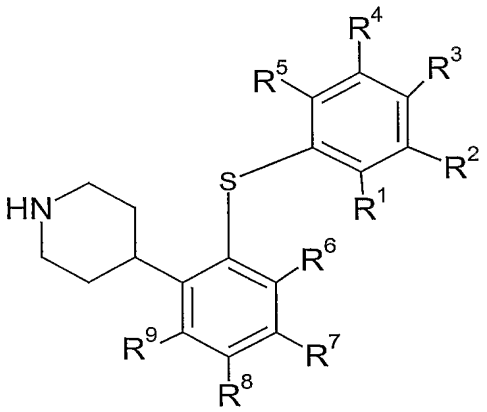
In the term C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{1-6}-alk(en/yn)yl are as defined above.

The term 3-7-membered ring optionally containing one further heteroatom, such as N, O, or S, as used herein refers to ring systems such as 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidinyl, 1-pyrrolyl or pyrazolyl, all of which may be further substituted with a group selected from a C_{1-6}-alk(en/yn)yl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl.

Description of the invention

The present invention relates to 4-(2-phenylsulfanyl-phenyl)-piperidine derivatives which are serotonin reuptake inhibitors and as such effective in the treatment of for example depression and anxiety.

Accordingly the present invention relates to a compound represented by the general formula I



I

wherein

R^1, R^2, R^3, R^4, R^5 are independently selected from hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, or NR^xR^y wherein R^x

and R^y are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or NR^zR^w-C_{1-6}-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

R^6, R^7, R^8, R^9 are independently selected from hydrogen, halogen, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or NR^zR^w-C_{1-6}-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

provided that at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 is different from hydrogen; also provided that when R^3 is methyl, then at least one of R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9 is different from hydrogen; or a salt thereof.

In one embodiment of the compound of formula I, R^1 is selected from hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, halo-C_{1-6}-alk(en/yn)yl, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or NR^zR^w-C_{1-6}-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, provided that if one of R^x and R^y is NR^zR^w-C_{1-6}-alk(en/yn)yl then the other is selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom. In a further embodiment of the compound of formula I R^1 is selected from hydrogen, halogen, cyano, C_{1-6}-

alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, halo-C_{1-6}-alk(en/yn)yl. In a further embodiment R^1 is NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, such as hydrogen, cyanomethyl, C_{1-6}-alk(en/yn)yl. In a further embodiment R^1 is NR^xR^y wherein R^x is NR^zR^w-C_{1-6}-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, and R^y is selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl. In a further embodiment R^1 is NR^xR^y wherein R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom, such as 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidinyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or more selected from a C_{1-6}-alk(en/yn)yl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, e.g. one or two selected from hydroxy, hydroxy-C_{1-6}-alkyl, C_{1-6}-alkyloxy-C_{1-6}-alkyl, C_{1-6}-alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. Typically, R^1 is selected from hydrogen; halogen; cyano; C_{1-6}-alkyl; C_{1-6}-alkyloxy; C_{1-6}-alkylsulfanyl; halo-C_{1-6}-alkyl; NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alkyl, cyanomethyl; NR^xR^y wherein R^y is selected from hydrogen, or C_{1-6}-alkyl, and R^x is NR^zR^w-C_{1-6}-alk(en/yn)yl wherein R^z and R^w are independently selected from hydrogen, or C_{1-6}-alkyl; 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidinyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or two selected from hydroxy, hydroxy-C_{1-6}-alkyl, C_{1-6}-alkyloxy-C_{1-6}-alkyl, C_{1-6}-alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. To further illustrate without limiting the invention an embodiment of R^1 is hydrogen; another embodiment of R^1 is C_{1-6}-alkyl, such as methyl; a further embodiment of R^1 is halogen, such as fluoro, or chloro.

In a further embodiment of the compound of formula I, R^2 is selected from hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, halo-C_{1-6}-alk(en/yn)yl. Typically, R^2 is selected from hydrogen, halogen, cyano, C_{1-6}-alkyl, C_{1-6}-alkyloxy, C_{1-6}-alkylsulfanyl, halo-C_{1-6}-alkyl. To further illustrate without

limiting the invention an embodiment of R^2 is hydrogen; another embodiment of R^2 is C_{1-6}-alkoxy, such as methoxy; a further embodiment of R^2 is halogen, such as fluoro, or chloro; a further embodiment of R^2 is C_{1-6}-alkyl, such as methyl.

In a further embodiment of the compound of formula I, R^3 is selected from hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, halo-C_{1-6}-alk(en/yn)yl. Typically, R^3 is selected from hydrogen, halogen, cyano, C_{1-6}-alkyl, C_{1-6}-alkyloxy, C_{1-6}-alkylsulfanyl, halo-C_{1-6}-alkyl. To further illustrate without limiting the invention an embodiment of R^3 is hydrogen; another embodiment of R^3 is C_{1-6}-alkyl, such as methyl; a further embodiment of R^3 is C_{1-6}-alkoxy, such as methoxy; a further embodiment of R^3 is halogen, such as bromo, chloro, or fluoro; a further embodiment of R^3 is halo-C_{1-6}-alkyl, such as CF_3; a further embodiment of R^3 is hydroxy-C_{1-6}-alkyl, such as hydroxy-methyl; a further embodiment of R^3 is NR^xR^y wherein R^x is hydrogen and R^y is C_{1-6}-alkyl, such as methylamino; a further embodiment of R^3 is C_{2-6}-alkenyl, such as ethenyl.

In a further embodiment of the compound of formula I, R^4 is selected from hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, halo-C_{1-6}-alk(en/yn)yl. Typically, R^4 is selected from hydrogen, halogen, cyano, C_{1-6}-alkyl, C_{1-6}-alkyloxy, C_{1-6}-alkylsulfanyl, halo-C_{1-6}-alkyl. To further illustrate without limiting the invention an embodiment of R^4 is hydrogen; another embodiment of R^4 is C_{1-6}-alkoxy, such as methoxy; a further embodiment of R^4 is halogen, such as fluoro, or chloro; a further embodiment of R^4 is C_{1-6}-alkyl, such as methyl.

In a further embodiment of the compound of formula I, R^5 is selected from hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, halo-C_{1-6}-alk(en/yn)yl, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or NR^zR^w-C_{1-6}-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, provided that if one of R^x and R^y is NR^zR^w-C_{1-6}-alk(en/yn)yl then the other is selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; or R^x and

R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom. In a further embodiment of the compound of formula I R^5 is selected from hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, halo-C_{1-6}-alk(en/yn)yl. In a further embodiment R^5 is NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, such as hydrogen, cyanomethyl, C_{1-6}-alk(en/yn)yl. In a further embodiment R^5 is NR^xR^y wherein R^x is NR^zR^w-C_{1-6}-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, and R^y is selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl. In a further embodiment R^5 is NR^xR^y wherein R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom, such as 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidinyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or more selected from a C_{1-6}-alk(en/yn)yl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, e.g. one or two selected from hydroxy, hydroxy-C_{1-6}-alkyl, C_{1-6}-alkyloxy-C_{1-6}-alkyl, C_{1-6}-alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. Typically, R^5 is selected from hydrogen; halogen; cyano; C_{1-6}-alkyl; C_{1-6}-alkyloxy; C_{1-6}-alkylsulfanyl; halo-C_{1-6}-alkyl; NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alkyl, cyanomethyl; NR^xR^y wherein R^y is selected from hydrogen, or C_{1-6}-alkyl, and R^x is NR^zR^w-C_{1-6}-alk(en/yn)yl wherein R^z and R^w are independently selected from hydrogen, or C_{1-6}-alkyl; 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidinyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or two selected from hydroxy, hydroxy-C_{1-6}-alkyl, C_{1-6}-alkyloxy-C_{1-6}-alkyl, C_{1-6}-alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. To further illustrate without limiting the invention an embodiment of R^5 is hydrogen; another embodiment of R^5 is C_{1-6}-alkyl, such as methyl; a further embodiment of R^5 is halogen, such as chloro, or fluoro.

In a further embodiment of the compound of formula I, R^6 is selected from hydrogen, halogen, C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl. Typically, R^6 is selected from hydrogen, halogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl. To further illustrate without limiting the invention an embodiment of R^6 is hydrogen; another embodiment of R^6 is halogen, such as fluoro.

In a further embodiment of the compound of formula I, R^7 is selected from hydrogen, halogen, C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl. Typically, R^7 is selected from hydrogen, halogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl. To further illustrate without limiting the invention an embodiment of R^7 is hydrogen; another embodiment of R^7 is halogen, such as fluoro.

In a further embodiment of the compound of formula I, R^8 is selected from hydrogen, halogen, C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or NR^zR^w-C_{1-6}-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, provided that if one of R^x and R^y is NR^zR^w-C_{1-6}-alk(en/yn)yl then the other is selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom. In a further embodiment of the compound of formula I, R^8 is selected from hydrogen, halogen, C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl. In a further embodiment, R^8 is NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, such as hydrogen, cyanomethyl, C_{1-6}-alk(en/yn)yl. In a further embodiment, R^8 is NR^xR^y wherein R^x is NR^zR^w-C_{1-6}-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, and R^y is selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl. In a further embodiment, R^8 is NR^xR^y wherein R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further

heteroatom, such as 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidinyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or more selected from a C_{1-6}-alk(en/yn)yl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy-C_{1-6}-alk(en/yn)yl, e.g. one or two selected from hydroxy, hydroxy-C_{1-6}-alkyl, C_{1-6}-alkyloxy-C_{1-6}-alkyl, C_{1-6}-alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. Typically, R^8 is selected from hydrogen; halogen; cyano; C_{1-6}-alkyl; C_{1-6}-alkyloxy; C_{1-6}-alkylsulfanyl; halo-C_{1-6}-alkyl; NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alkyl, cyanomethyl; NR^xR^y wherein R^y is selected from hydrogen, or C_{1-6}-alkyl, and R^x is NR^zR^w-C_{1-6}-alk(en/yn)yl wherein R^z and R^w are independently selected from hydrogen, or C_{1-6}-alkyl; 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidinyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or two selected from hydroxy, hydroxy-C_{1-6}-alkyl, C_{1-6}-alkyloxy-C_{1-6}-alkyl, C_{1-6}-alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. To further illustrate without limiting the invention an embodiment of R^8 is hydrogen; another embodiment of R^8 is halogen, such as fluoro, or bromo; a further embodiment of R^8 is C_{1-6}-alkyl, such as methyl; another embodiment of R^8 is C_{1-6}-alkyloxy, such as methoxy; a further embodiment of R^8 is halo-C_{1-6}-alkyl, such as CF_3.

In a further embodiment of the compound of formula I, R^9 is selected from hydrogen, halogen, C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl. Typically, R^9 is selected from hydrogen, halogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl. To further illustrate without limiting the invention an embodiment of R^9 is hydrogen; another embodiment of R^9 is halogen, such as fluoro.

Typically, the compound of formula I has at least one substituent in the phenyl ring(s), selected from any one of R^1-R^9, which is different from hydrogen, such as 1, 2, 3, or 4 substituents in the phenyl ring(s), selected from any one of R^1-R^9, which is/are different from hydrogen, and the remaining substituents are hydrogen. Thus, in a further embodiment 1 substituent selected from any one of R^1-R^9, which is different from hydrogen, is present in either of the two phenyl rings, such as 1 substituent selected from R^1-R^5, or the substituent is selected from R^6-R^9. In a further

embodiment, 2 substituents selected from R^1-R^9, which are different from hydrogen, are present in either of the two phenyl rings, such as 1 substituent selected from R^1-R^5, and the other selected from R^6-R^9, or both substituents are selected from R^1-R^5. In a further embodiment, 3 substituents selected from R^1-R^9, which are different from hydrogen, are present in either of the two phenyl rings, such as 2 substituents selected from R^1-R^5, and the last substituent is selected from R^6-R^9. In each embodiment, as mentioned the remaining substituents are hydrogen. To illustrate this further without limiting the invention, some typical embodiments are outlined hereafter.

Thus, in a further embodiment of the compound of formula I one substituent is present which is R^2 as defined above, except hydrogen. In a further embodiment of the compound of formula I, one substituent is present which is R^3 as defined above, except hydrogen. In a further embodiment of the compound of formula I, two substituents are present being R^3 and R^8, wherein R^3 and R^8 are as defined above, except hydrogen. In a further embodiment of the compound of formula I, two substituents are present being R^3 and R^6, wherein R^3 and R^6 are as defined above, except hydrogen. In a further embodiment of the compound of formula I, two substituents are present being R^3 and R^7, wherein R^3 and R^7 are as defined above, except hydrogen. In a further embodiment of the compound of formula I, two substituents are present being R^1 and R^3, wherein R^1 and R^3 are as defined above, except hydrogen. In a further embodiment of the compound of formula I, two substituents are present being R^2 and R^3, wherein R^2 and R^3 are as defined above, except hydrogen. In a further embodiment of the compound of formula I, three substituents are present being R^1, R^3 and R^8, wherein R^1, R^3 and R^8 are as defined above, except hydrogen. In each embodiment, as mentioned above the remaining substituents are hydrogen.

In a further embodiment of the compound of formula I, said compound is selected from

4-[2-(4-Chloro-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-piperidine

4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine

4-[2-(4-Chloro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(4-Methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Fluoro-2-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Chloro-2-methyl-phenylsulfanyl)-phenyl]-piperidine

4-[2-(4-Chloro-2-fluoro-phenylsulfanyl)-phenyl]-piperidine

4-[2-(2,4-Dichloro-phenylsulfanyl)-phenyl]-piperidine

4-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-phenyl]-piperidine

4-[2-(4-Chloro-phenylsulfanyl)-phenyl- piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-3-fluoro-phenyl]-piperidine

4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-bromo-phenyl]-piperidine

4-[2-(4-Methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Methyl-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine

4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-4-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Methyl-4-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(3-Methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-4-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-2-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-4-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2,4-Dichloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2,4-Difluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2,4-Dimethyl-phenylsulfanyl)-3-fluoro-phenyl]-piperidine

4-[2-(Phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Bromo-2-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(3-Chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(3-Fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-4-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Methyl-4-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Trifluoromethyl-phenylsulfanyl)-phenyl]-

4-[2-(2-Chloro-4-fluoro-phenylsulfanyl)-phenyl]-piperidine

4-[2-(4-Methoxy-2-methyl-phenylsulfanyl)-phenyl]-piperidine

4-[2-(2,4-Difluoro-phenylsulfanyl)-phenyl]-piperidine

4-[2-(2,3-Dimethyl-phenylsulfanyl)-phenyl]-piperidine

4-[2-(3,4-Dimethyl-phenylsulfanyl)-phenyl]-piperidine

4-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(2-Chloro-4-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(2-Fluoro-4-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Fluoro-3-methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(3-Fluoro-2-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(3-Fluoro-4-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(5-Chloro-2-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(2-Chloro-4-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(3-Methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Chloro-2-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(3-Chloro-2-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(2,4-Difluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Methyl-phenylsulfanyl)-5-methoxy-phenyl]-piperidine

4-[2-(4-Fluoro-phenylsulfanyl)-5-methoxy-phenyl]-piperidine

4-[2-(2-Methyl-4-methoxy-phenylsulfanyl)-5-methoxy-phenyl]-piperidine

4-[2-(4-Fluoro-2-methyl-phenylsulfanyl)-5-methoxy-phenyl]-piperidine

4-[2-(3-Methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Methoxy-2-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-2-Methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Fluoro-4-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2,3-Dimethyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Fluoro-2-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Chloro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-3-methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-4-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-2-fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Trifluoromethyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Chloro-2-fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3,4-Dimethyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-4-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2,4-Dichloro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-4-methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2,4-Difluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2,3-Dichloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Trifluoromethoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-2-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Trifluoromethyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(3-Methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-2-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2,3-Dimethyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-ylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-3-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine
4-[2-(3,4-Dimethyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine
4-[2-(2-Chloro-4-Methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine
4-[2-(2-Fluoro-4-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine
4-[2-(5-Chloro-2-fluoro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine
4-[2-(2-Chloro-4-fluoro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine
4-[2-(2,3-Dimethyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine
4-[2-(3-Fluoro-2-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine
4-[2-(4-Methoxy-2-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine
4-[2-(3-Fluoro-4-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine
4-[2-(4-Fluoro-2-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine
4-[2-(4-Hydroxymethyl-phenylsulfanyl)-phenyl]-piperidine
4-[2-(2-Fluoro-4-methyl-amine-phenylsulfanyl)-5-fluorophenyl]-piperidine
4-[2-(2-Fluoro-4-vinyl-phenylsulfanyl)-5-fluorophenyl]-piperidine,
or a pharmaceutically acceptable salt thereof. Each of these compounds is considered a specific embodiment and may be subject to individual claims.

As mentioned above, the present compounds of formula I are serotonin reuptake inhibitors. Some of the tested compounds have also shown good affinity to the $5HT_{2C}$ receptor, typically Ki < 75 nM as measured in the test described in the examples section, and such compounds are considered to be further aspects of the invention. Accordingly, in a further aspect the present invention relates to a compound of formula I or a salt thereof, wherein R^3 is selected from C_{1-6} alkoxy (such as methoxy), halogen (such as Cl), or halo-C_{1-6} alkyl (such as CF_3), and R^1, R^2, and R^4-R^9 are all hydrogen. In a still further aspect, the present invention relates to a compound of formula I or a salt thereof, wherein R^1 is selected from halogen (such as Cl or F), and R^3 is selected from halogen (such as F), and R^2, and R^4-R^9 are all hydrogen. In a still further aspect, the present invention relates to a compound of formula I or a salt thereof, wherein R^1 is selected from halogen (such as Cl), and R^7 is selected from halogen (such as F), and R^2-R^6 and R^8-R^9 are all hydrogen. In a still further aspect, the present invention relates to a compound of formula I or a salt thereof, wherein R^3 is selected from halogen (such as F), and R^7 is selected from halogen (such as F), and R^1-R^2, R^4-R^6 and R^8-R^9 are all hydrogen. In a still further aspect, the present invention

relates to a compound of formula I or a salt thereof, wherein R^1 is selected from halogen (such as F), and R^9 is selected from halogen (such as F), and R^2-R^8, are all hydrogen. In a still further aspect, the present invention relates to a compound of formula I or a salt thereof, wherein R^2 is selected from halogen (such as Cl or F), and R^9 is selected from halogen (such as F), and R^1 and R^3-R^8, are all hydrogen. In a still further aspect, the present invention relates to a compound of formula I or a salt thereof, wherein R^3 is selected from C_{1-6} alkyl (such as methyl), C_{1-6} alkoxy (such as methoxy), or halogen (such as Cl or F), and R^9 is selected from halogen (such as F), and R^1, R^2, and R^4-R^8, are all hydrogen. In a still further aspect, the present invention relates to a compound of formula I or a salt thereof, wherein R^3 is selected from C_{1-6} alkoxy (such as methoxy), and R^6 is selected from halogen (such as F), and R^1, R^2, R^4, R^5, and R^7-R^9 are all hydrogen. In a still further aspect, the present invention relates to a compound of formula I or a salt thereof, wherein R^3 is selected from C_{1-6} alkoxy (such as methoxy), or halogen (such as Cl), and R^7 is selected from halogen (such as F), and R^1, R^2, R^4-R^6, and R^8-R^9 are all hydrogen. In a still further aspect, the present invention relates to a compound of formula I or a salt thereof, wherein R^3 is selected from C_{1-6} alkyl (such as methyl), C_{1-6} alkoxy (such as methoxy), or halogen (such as F or Cl), and R^8 is selected from C_{1-6} alkyl (such as methyl), C_{1-6} alkoxy (such as methoxy), or halogen (such as F), and R^1, R^2, R^4-R^7, and R^9 are all hydrogen. In a still further aspect, the present invention relates to a compound of formula I or a salt thereof, wherein R^1 is selected from C_{1-6} alkyl (such as methyl), R^3 is selected from C_{1-6} alkyl (such as methyl), and R^6 is selected from halogen (such as F), and R^2, R^4-R^5, and R^7-R^9 are all hydrogen. In a still further aspect, the present invention relates to a compound of formula I or a salt thereof, wherein R^1 is selected from C_{1-6} alkyl (such as methyl), or halogen (such as F), R^3 is selected from C_{1-6} alkoxy (such as methoxy), or halogen (such as F, Br, or Cl), and R^8 is selected from C_{1-6} alkyl (such as methyl), or halogen (such as F), and R^2, R^4-R^7, and R^9 are all hydrogen. In a still further aspect, the present invention relates to a compound of formula I or a salt thereof, wherein R^1 is selected from C_{1-6} alkyl (such as methyl), or halogen (such as F or Cl), R^3 is selected from C_{1-6} alkyl (such as methyl), C_{1-6} alkoxy (such as methoxy), or halogen (such as F, or Cl), and R^9 is selected from halogen (such as F), and R^2, and R^4-R^8, are all hydrogen. In a still further aspect, the present invention relates to a compound of formula I or a salt thereof, wherein R^1 is selected from halogen (such as F), R^2 is

selected from halogen (such as Cl), and R^9 is selected from halogen (such as F), and R^3, and R^4-R^8, are all hydrogen. In a still further aspect, the present invention relates to a compound of formula I or a salt thereof, wherein R^2 is selected from C_{1-6} alkoxy (such as methoxy), or halogen (such as F), R^3 is selected from halogen (such as F), or C_{1-6} alkyl (such as methyl), and R^9 is selected from halogen (such as F), and R^1, and R^4-R^8, are all hydrogen. Preferred compounds which are serotonin reuptake inhibitors and has shown good affinity to the $5HT_{2C}$ receptor are selected from:

4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-piperidine

4-[2-(4-Chloro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(4-Methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Fluoro-2-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Chloro-phenylsulfanyl)-phenyl- piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-3-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-2-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-4-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2,4-Difluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2,4-Dimethyl-phenylsulfanyl)-3-fluoro-phenyl]-piperidine

4-[2-(4-Bromo-2-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-4-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-4-fluoro-phenylsulfanyl)-phenyl]-piperidine

4-[2-(2,4-Difluoro-phenylsulfanyl)-phenyl]-piperidine

4-[2-(4-Fluoro-phenylsulfanyl)-5-methoxy-phenyl]-piperidine

4-[2-(4-Methoxy-2-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Fluoro-4-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Chloro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-3-methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-2-fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine
4-[2-(4-Trifluoromethyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine
4-[2-(3-Chloro-2-fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine
4-[2-(4-Methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine
4-[2-(4-Chloro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine
4-[2-(2-Fluoro-4-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine
4-[2-(2-Fluoro-4-methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine
4-[2-(2,4-Difluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine
4-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine
4-[2-(4-Methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine
4-[2-(4-Fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine
4-[2-(2-Chloro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine
4-[2-(4-Fluoro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine,
or a pharmaceutically acceptable salt thereof.

The present invention also comprises salts of the present compounds, typically, pharmaceutically acceptable salts. Such salts include pharmaceutical acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids.

Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, itaconic, lactic, methanesulfonic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methane sulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline and the like.

Examples of metal salts include lithium, sodium, potassium, magnesium salts and the

like.

Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, *n*-butyl-, *sec*-butyl-, *tert*-butyl-, tetramethylammonium salts and the like.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers (i.e. enantiomers or diastereomers), as separated, pure or partially purified optical isomers and any mixtures thereof including racemic mixtures are included within the scope of the invention.

Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can also be resolved into their optical antipodes, e.g. by fractional crystallization of d- or l- (tartrates, mandelates or camphorsulphonate) salts. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by Collet and Wilen in the textbook *Enantiomers, Racemates, and Resolutions*, John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials, or by stereo selective synthesis.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms that the compounds are able to form are included within the scope of the present invention.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of the compounds of the general formula (I), which are readily convertible in vivo into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in the textbook *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

As mentioned above, the compounds of formula I are serotonin reuptake inhibitors, and accordingly may be applicable for the treatment, including prevention, of affective disorders, such as depression, anxiety disorders including general anxiety disorder and panic disorder and obsessive compulsive disorder.

Accordingly, in a further aspect the invention relates to a compound of formula I for use as a medicament.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier or diluent. The composition may comprise any one of the embodiments of formula I described above.

In an embodiment of the pharmaceutical composition, the compound of formula I is present in an amount of from about 0.001 to about 100 mg/kg body weight per day.

The present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of a disease or disorder, wherein a serotonin reuptake inhibitor is beneficial. The medicament may comprise any one of the embodiments of formula I described above.

In particular, the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of affective disorders.

In a further embodiment, the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of depression.

In a further embodiment, the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of anxiety disorders.

In a further embodiment, the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of general anxiety disorder.

In a further embodiment, the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of social anxiety disorder.

In a further embodiment, the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of post traumatic stress disorder.

In a further embodiment, the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of obsessive compulsive disorder.

In a further embodiment, the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of panic disorder.

In a further embodiment, the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of panic attacks.

In a further embodiment, the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of specific phobias.

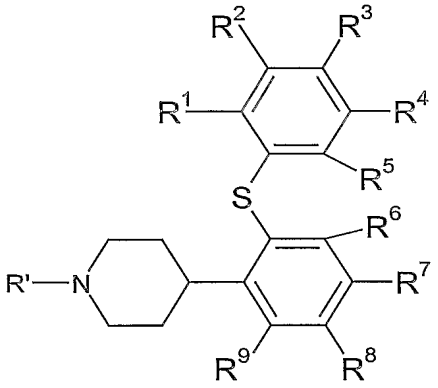
In a further embodiment, the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of social phobia.

In a further embodiment, the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of agoraphobia.

A further aspect of the invention relates to a method for the treatment of a disease or disorder selected from the group consisting of an affective disorder, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia in a living animal body, including a human, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I.

In a further aspect, the present invention relates to a method of preparing a compound of formula I, comprising

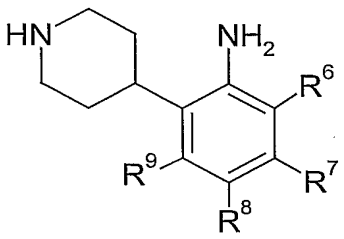
a) Deprotection or cleavage from a polymer support of a compound with formula II



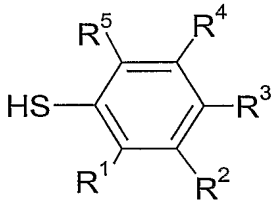
II

wherein R^1-R^9 are as previously described, and R' is a carbamate (such as methyl-, ethyl-, *tert*-butyl-, allyl-, or benzyl-carbamate) or a benzyl-derived protective group, wherein the protective groups may be linked to a solid support, for example the Wang resin-based carbamate linker; or

b) Chemical transformation of a compound with formula III to the corresponding diazonium compound and subsequent reaction with a thiophenol of formula IV



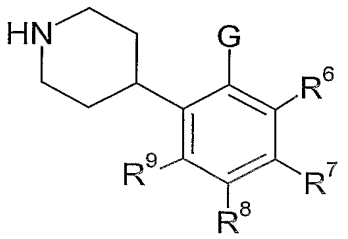
III



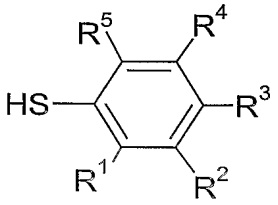
IV

wherein R^1-R^9 are as previously described; or

c) Reacting a compound of formula V with a thiophenol of formula IV in the presence of a palladium or copper catalyst



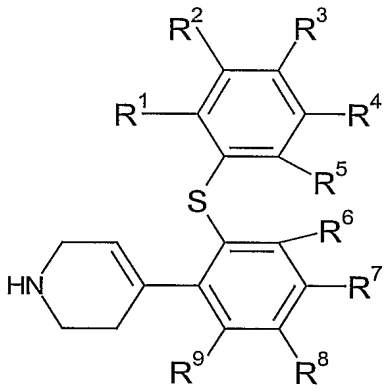
V



IV

wherein R^1-R^9 are as previously described, and G is a chlorine, bromine, or iodine atom or a sulfonyl ester, wherein the sulfonyl ester is derived from the corresponding phenol by reaction with 4-methyl-benzenesulfonyl chloride, trifluoro-methanesulfonic acid anhydride, 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonyl fluoride, or related compounds; or

d) Hydrogenate the double bond in a compound of formula VI



VI

wherein R^1-R^9 are as described above.

Pharmaceutical compositions

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses.

The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in the textbook *Remington: The Science and Practice of Pharmacy*, 19 Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen. Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body

weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain from 0.01 to about 1000 mg, preferably from about 0.05 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound of the formula (I) contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the formula (I) with a chemical equivalent of a pharmaceutically acceptable acid. Representative examples are mentioned above.

For parenteral administration, solutions of the novel compounds of the formula (I) in sterile aqueous solution, aqueous propylene glycol, aqueous vitamin E or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid and lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospho lipids, fatty acids, fatty acid amines, polyoxyethylene and water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the novel compounds of the formula (I) and the pharmaceutical acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. Furthermore, the orally available formulations may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

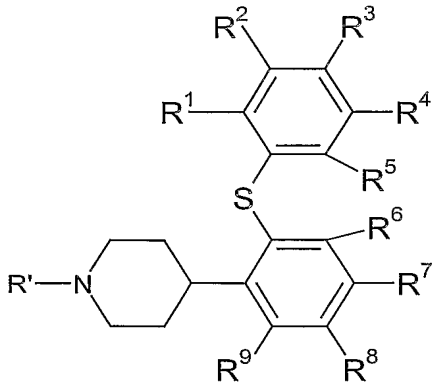
If a solid carrier is used for oral administration, the preparation may be a tablet, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge.

The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g.

If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

The compounds of the invention are prepared by the following general methods:

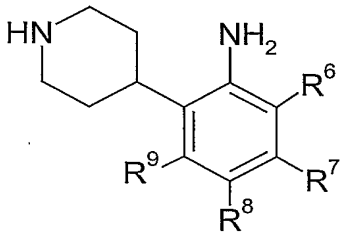
a) Deprotection or cleavage from a polymer support of a compound with formula II



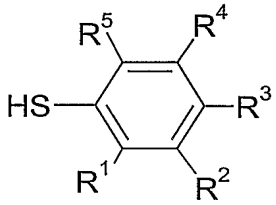
II

wherein R^1-R^9 are as previously described, and R' is a carbamate or a benzyl-derived protective group. These protective groups may be linked to a solid support, for example the Wang resin-based carbamate linker.

b) Chemical transformation of a compound with formula III to the corresponding diazonium compound and subsequent reaction with a thiophenol of formula IV



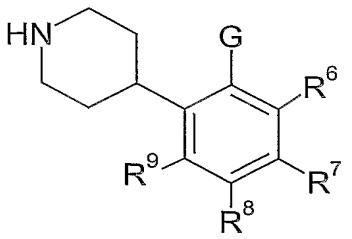
III



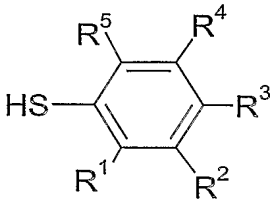
IV

wherein R^1-R^9 are as previously described.

c) Reacting a compound of formula V with a thiophenol of formula IV in the presence of a palladium or copper catalyst



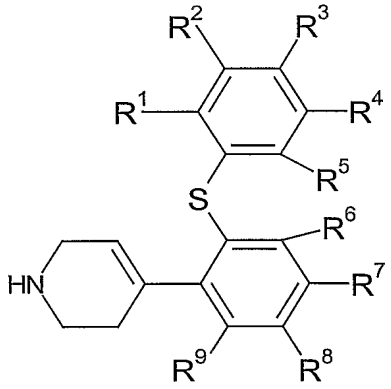
V



IV

wherein R^1-R^9 are as previously described, and G is a chlorine, bromine, or iodine atom or a sulfonyl ester. The sulfonyl ester is derived from the corresponding phenol by reaction with 4-methyl-benzenesulfonyl chloride, trifluoro-methanesulfonic acid anhydride, 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonyl fluoride, or related compounds; or

d) Hydrogenate the double bond in a compound of formula VI

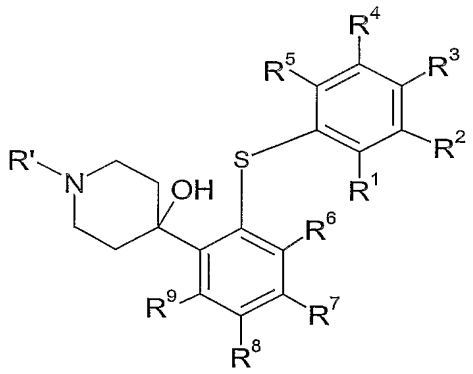


VI

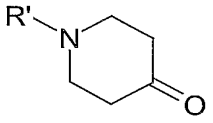
wherein R^1-R^9 are as described above.

The deprotection according to method a) was performed by standard techniques, known to the persons skilled in the art and detailed in the textbook *Protective Groups in Organic Synthesis*, Greene and Wuts, Wiley Interscience, (1991), ISBN 0471623016. The cleavage from a polymer support, such as from the Wang resin based carbamate linker, according to method a) was performed according to literature

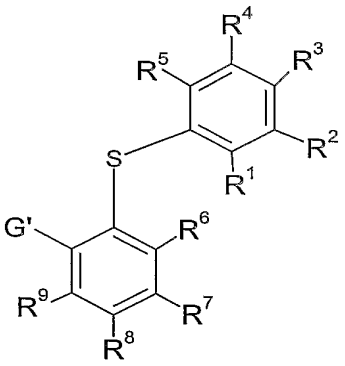
known procedures (Zaragoza *Tetrahedron Lett.* **1995**, *36*, 8677-8678 and Conti *et al. Tetrahedron Lett.* **1997**, *38*, 2915-2918).



VII



VIII



IX

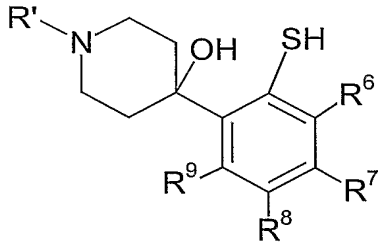
Compounds of formula II can be prepared by dehydrating a compound of formula VII under conditions that do not lead to cleavage of the N-R' bond followed by hydrogenation of the double bond. Alternatively, compounds of formula VII can be dehydrated with subsequent or concomitant cleavage of the N-R' bond to provide compounds of formula VI; subsequent protection of the amino group and hydrogenation of the double bond then provides compounds of formula II. The reduction of the double bond may be performed using standard heterogeneous hydrogenation procedures or using homogeneous hydrogenation methods such as e.g. Crabtree's or Wilkinson's catalysts (see e.g *Encyclopedia of Reagents for Organic Synthesis*, Paquette (Ed.), Wiley (1995), ISBN 0471936235, p. 1447 and p 1253, respectively), or vice-versa. The dehydration reaction and optional deprotection of a compound of formula VII to yield compounds II or VI was performed in a similar manner as described in Palmer *et al. J. Med. Chem.* **1997**, *40*, 1982-1989.

The starting material of formula VII wherein R'=H was prepared from a compound of formula VII wherein R' is a carbamate or benzyl-derived protective group by deprotection under standard conditions known to the persons skilled in the art and detailed in the textbook *Protective Groups in Organic Synthesis*, Greene and Wuts, Wiley Interscience, (1991), ISBN 0471623016. Compounds of formula VII wherein R' = *tert*-butyl oxo carbonyl (BOC), may be prepared as described in Palmer *et al. J.*

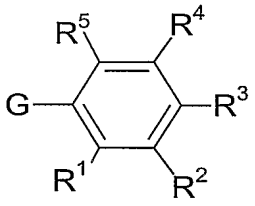
Med. Chem. **1997**, *40*, 1982-1989. Compounds VII were prepared from the corresponding properly substituted 1-bromo-phenylsulfanylbenzenes or 1-iodo-phenylsulfanylbenzenes of formula IX by metal-halogen exchange followed by addition of an appropriate electrophile of the formula VIII in a similar manner as described in Palmer et *al. J. Med. Chem.* **1997**, *40*, 1982-1989 or by following the procedures of Kitagawa *et al. Angew. Chem. Int. Ed.* **2000**, *39*, 2481-2483, or of Boymond *et al. Angew. Chem. Int. Ed.* **1998**, *37*, 1701-1703. Compounds VII, VIII, and IX have R^1-R^9 and R' as previously described, and G' is a bromine or iodine atom. The properly substituted 1-bromo-phenylsulfanylbenzenes or 1-iodo-phenylsulfanylbenzenes were prepared from thiophenols IV and properly substituted aryliodides or aryl bromides according to the general procedures by Schopfer and Schlapbach *Tetrahedron* **2001**, *57,* 3069-3073; Bates *et al. Org. Lett.* **2002**, *4*, 2803-2806 and Kwong *et al. Org. Lett.* 2002, *4*, 581-584.

Starting materials of formula VII can also be prepared by palladium or copper catalysed coupling of a thiophenol of formula X with a compound of formula XI according to Schopfer and Schlapbach *Tetrahedron* **2001**, *57,* 3069-3073; Bates *et al. Org. Lett.* **2002**, *4*, 2803-2806, or Kwong *et al. Org. Lett.* 2002, *4*, 581-584. Compounds X can be prepared by ortholithiation of compounds IV, or by metal-halogen exchange of properly substituted 2-bromo-thiophenol or 2-iodo-thiophenol derivatives, followed by addition of electrophile of formula VIII, as exemplified in the experimental. Compounds of formula X and XI have R^1-R^9, R', and G as described previously. The sulfonyl esters can be derived from the corresponding phenol by reaction with 4-methyl-benzenesulfonyl chloride, trifluoro-methanesulfonic acid anhydride, 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonyl fluoride, or related compounds, as described by e.g. Cho *et al. J. Org. Chem.*, **2003**, *68*, 3017-3025, Arnould *et al. Tetrahedron Lett.* **1996**, *37*, 45-23-4524, and Anderson *et al. J. Org. Chem.* **2003**, *68*, 9563-9573. The phenol in terms can be prepared from the analogous anisole or suitably protected phenol by standard techniques, known to the persons skilled in the art and detailed in the textbook *Protective Groups in Organic Synthesis*, Greene and Wuts, Wiley Interscience, (1991), ISBN 0471623016.

Starting materials of formula V and XI can be prepared by diazotation of properly substituted aniline derivatives followed by addition of either copper bromide or copper iodide as described in the textbook *Advanced Organic Chemistry* March, John Wiley & Sons (1992), ISBN 0471601802, by diazotation of the corresponding aniline derivative followed by addition of potassium iodide as described by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753, or by diazotization under the conditions reported by Doyle *et al. J. Org. Chem.* **1977**, *42*, 2426-2431 and Doyle *et al. J. Org. Chem.* **1980**, *45*, 2570-2575. Alternatively, compound V in which G is a sulfonyl ester may be derived from the corresponding phenol as described above for compound XI. The phenol in terms can be prepared from the analogous anisole or suitably protected phenol by standard techniques, known to the persons skilled in the art and detailed in the textbook *Protective Groups in Organic Synthesis*, Greene and Wuts, Wiley Interscience, (1991), ISBN 0471623016.

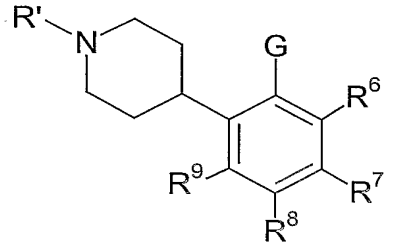


X

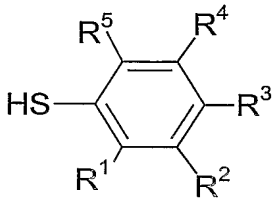


XI

Compounds II can also be prepared by removal of the hydroxyl group from compounds VII using standard deoxygenation procedures (e.g. Barton-type reduction). One example of this uses activation with methyl oxalyl chloride followed by reduction with tri-*n*-butyltin hydride and 2-[(cyano-dimethyl-methyl)-azo]-2-methyl-propionitrile (AIBN) as described by Hansen *et al. Synthesis* **1999**, 1925-1930. Alternatively, one can use trifluoro-acetic acid and triethyl-silane or use sodium borohydride or related reducing reagents as described in the textbook *Reductions in Organic Chemistry*, Hudlicky, ACS Monograph 188, The American Chemical Society (1996), ISBN 0841233446.

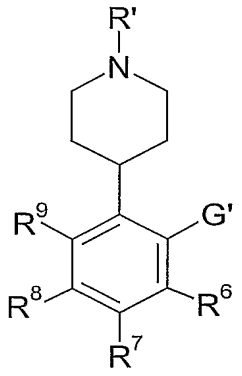


XII

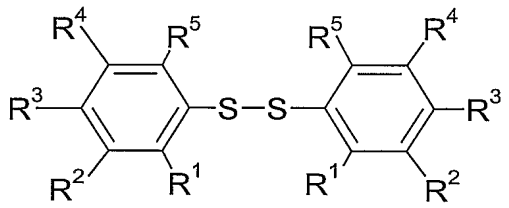


IV

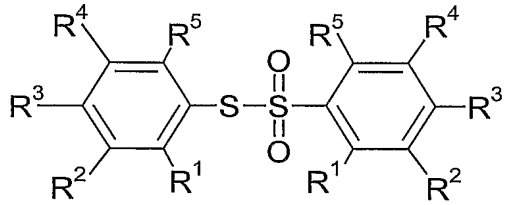
Compounds II can also be prepared by reacting compound XII with thiophenol IV in the presence of a palladium or copper catalyst using the methods described previously for compounds X and XI. Compound XII has R^6-R^9, R', and G are as defined previously. Compound XII may be prepared from compound III via the general diazotization methods outlined for compounds V and IX below, or from compound XX as discussed below.



XIII



XIV



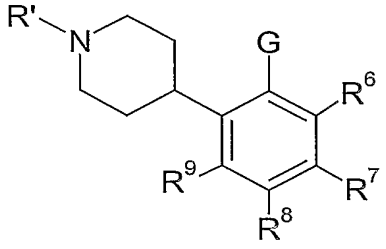
XV

Compounds II can also be prepared by reacting compound XIII with an alkyl metal species followed by reaction with disulfide XIV, e.g. via the method reported by Carreno *et al. Tetrahedron*, **1991**, *47*, 605-614. Alternatively, the metallated species derived from compounds XIII may be quenched with compounds of formula XV according to the procedure of Marchand *et al. Tetrahedron* **2000**, *56*, 7331-7338. Compounds XIV and XV are either commercially available or can be prepared from thiophenols IV, e.g. via the methods described in the the textbook *Advanced Organic Chemistry* March, John Wiley & Sons (1992), ISBN 0471601802, or by the

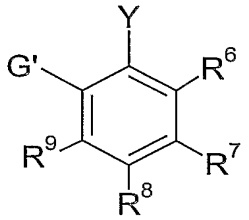
procedures reported by Barnard *J. Chem. Soc.* **1957**, 4673-4675, Miller *J. Chem. Soc.* **1925**, 224-233, or Evans *et al. J. Org. Chem.* **1990**, *55*, 2337-2344. Compounds XIII can be prepared using the same techniques as discussed for compounds XII. For compounds XIII and XIV, R^1-R^9, R', and G' are as defined previously.

Diazotation of compound III followed by reaction with a thiophenol IV to yield compound I can be performed by addition of the diazonium salt of the corresponding aniline to a solution of sodium salt of a thiophenol in an aqueous suspension of copper under conditions similar to those described for starting material XI below. The starting material of formula III are either commercially available or can be prepared by methods analogues to those described in the literature (e.g. Berridge, M. S. *et al. J. Med. Chem.* **1993**, *36*, 1284-1290). Thiophenols IV are either commercially available or can be prepared according to methods described in standard works such as Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc. New York, or from compounds XI using the methods of Arnould *et al. Tetrahedron Lett.* **1996**, *37*, 4523-4524 and Rane *et al. Tetrahedron Lett.* **1994**, 35, 3225-3226 followed by deprotection under standard conditions known to the persons skilled in the art and detailed in the textbook *Protective Groups in Organic Synthesis*, Greene and Wuts, Wiley Interscience, (1991), ISBN 0471623016.

The coupling of a compound of formula V with a thiophenol of formula IV according to method c) was performed in the presence of a palladium or copper catalyst e.g. by using the method described by Schopfer and Schlapbach *Tetrahedron* **2001**, *57*, 3069-307, Bates *et al. Org. Lett.* **2002**, *4*, 2803-2806, or Kwong *et al. Org. Lett.* **2002**, *4*, 581-584.

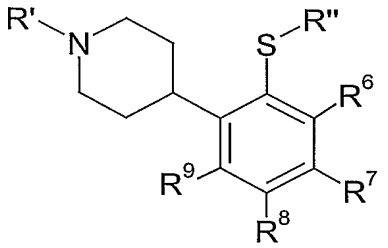


XVII

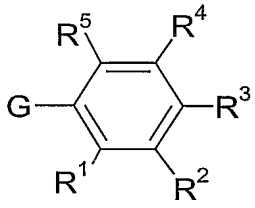


XVI

Compounds V can be prepared by from compounds XII by N-deprotection using standard techniques, known to the persons skilled in the art and detailed in the textbook *Protective Groups in Organic Synthesis*, Greene and Wuts, Wiley Interscience, (1991), ISBN 0471623016. Compounds XVII can be derived from compounds XVI by palladium catalysed reaction with 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (or related boronic acid derivatives) using the method of Eastwood *Tetrahedron Lett.* **2000**, *41*, 3705-3708 or by using the conditions for the Suzuki coupling reported by Zhuravel and Nguyen *Tetrahedron Lett.* **2001**, *42*, 7925-7928 as exemplified in the experimental followed by reduction of the double bond as described previously. Compounds of formula XVI have R^6-R^9, and G' as described above, while Y is either a chlorine, bromine, or iodine atom or a hydroxyl group, or a methoxy group or



XVII

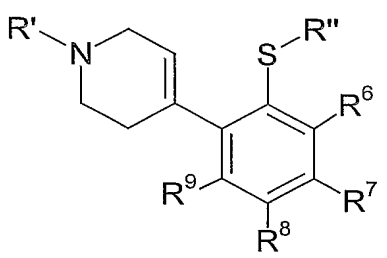


XI

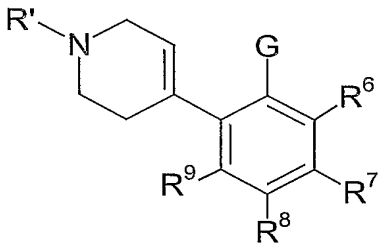
alternatively protected hydroxyl group that can be deprotected under conditions, known to the persons skilled in the art and detailed in the textbook *Protective Groups in Organic Synthesis*, Greene and Wuts, Wiley Interscience, (1991), ISBN 0471623016, or a sulfonyl ester as described for compounds of formula XI.

Compounds of formula II can further be prepared by coupling of compounds of structures XVII when R'' is a hydrogen and compound XI in the presence of a suitable palladium or copper catalyst as described by Schopfer and Schlapbach *Tetrahedron* **2001**, *57*, 3069-3073; Bates *et al. Org. Lett.* **2002**, *4*, 2803-2806 or Kwong *et al. Org. Lett.* 2002, *4*, 581-584. Compound XVII has R^6-R^9, and R' as defined previously, and R'' is a hydrogen or a trialkyl, a dialkylaryl, a alkyldiaryl silyl protection group. Compounds of formula XVII for which R'' is a silyl group can be prepared from compounds of formula XII under the conditions reported by Arnould *et*

al. Tetrahedron Lett. **1996**, *37*, 45-23-4524 and Rane *et al. Tetrahedron Lett.* **1994**, 35, 3225-3226. The coupling of compounds XVII and XI when R'' is a silyl group can be effected by the use of copper or palladium catalyst in the presence of a stoichiometric amount of fluoride ions, e.g. in the form of tetra-*n*-butyl ammonium fluoride (TBAF) under conditions closely related to those reported by Arnould *et al. Tetrahedron Lett.* **1996**, *37*, 45-23-4524 and Rane *et al. Tetrahedron Lett.* **1994**, 35, 3225-3226 as detailed in the experimental.



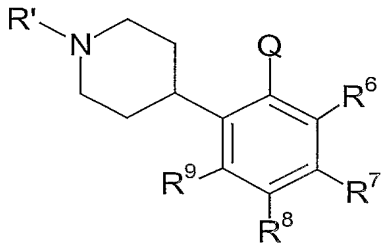
XVIII



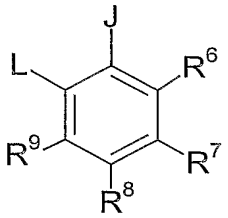
XX

Compounds of formula II can be prepared by coupling of compounds XVIII and XI in the presence of a suitable copper or palladium catalyst as detailed for the analogous coupling of compounds XVII and XI above, followed by reduction of the double bond under the conditions outlined above for compound VI. Compounds XVIII have R^6-R^9, R', and R'' as defined previously. Compounds of formula XVIII for which R'' is a silyl group can be prepared from compounds of formula XX wherein R^6-R^9, R', and G are as defined above under the conditions reported by Arnould *et al. Tetrahedron Lett.* **1996**, *37*, 4523-4524 and Rane *et al. Tetrahedron Lett.* **1994**, 35, 3225-3226. Compound XX can be derived from compound XVI by copper or palladium catalysed reaction with 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (or related boronic acid derivatives) as described by Eastwood *Tetrahedron Lett.* **2000**, *41*, 3705-3708 or by using the conditions for the Suzuki coupling reported by Zhuravel and Nguyen *Tetrahedron Lett.* **2001**, *42*, 7925-7928 as exemplified in the experimental. Alternatively, compound XX can be derived from compound XXI by directed ortho lithiation (L = hydrogen) or halide-lithium exchange (L = iodide or bromide), trapping with electrophile VIII as described for compound XXII below, followed by an elimination-

protection sequence as previously described for compounds VII. For compounds XXI



XXII



XXI

R^6-R^9 are as defined above while J is a methoxy group or a similarly directing hydroxyl derivative, and L is a hydrogen, bromide, or iodide atom.

Compound X may be prepared from compounds XXI by directed ortho lithiation or halide-metal exchange according to the methods reported by Palmer et *al. J. Med. Chem.* **1997**, *40*, 1982-1989, Kitagawa *et al. Angew. Chem. Int. Ed.* **2000**, *39*, 2481-2483, or Boymond *et al. Angew. Chem. Int. Ed.* **1998**, *37*, 1701-1703, or according to the procedures reported in the textbook *Organometallics in Synthesis. A Manual*, Schlosser (Ed), John Wiley & Sons, Ltd (2002), ISBN 0471984167 followed by quenching with eletrophiles of the formula VIII. Upon deoxygenation or elimination-reduction as described above for compound VII, compounds XXI may be transformed into compounds XXII for which R^6-R^9 are as defined above, and Q is an sulfonyl ester as described for compounds XI. Hence, compounds XXII can be transformed into compounds XVII under the conditions described for compounds XVII. The product of the reaction of the lithiated compound XXI and the electrophile VIII can be activated as a sulfonyl ester after transformation of J into a hydroxyl group by methods known to the persons skilled in the art and detailed in the textbook *Protective Groups in Organic Synthesis*, Greene and Wuts, Wiley Interscience, (1991), ISBN 0471623016. The resulting sulfonyl esters can be transformed into compounds X under the conditions discussed for compounds XVII followed by cleavage of the silyl protective group by methods known to the persons skilled in the art and detailed in the textbook *Protective Groups in Organic Synthesis*, Greene and Wuts, Wiley Interscience, (1991), ISBN 0471623016.

The reduction of the double bond according to method d) was generally performed by catalytic hydrogenation at low pressure (< 3 bar) in a Parr shaker apparatus. Starting material of formula VI may be prepared from compounds of formula VII.

Examples

Analytical LC-TOF data were obtained on a 4 channel Micromass LCT instrument equipped with MUX electrospay source and Waters 1525 LC system. Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. Column: 30 X 4.6 mm Waters Symmmetry C18 column with 3.5 µm particle size; Solvent system: A = water/TFA (100:0.05) and B = water/acetonitrile/TFA (5:95:0.03) (TFA = trifluoro-acetic acid); Method: Linear gradient elution with 90% A to 100% B in 4 min and with a flow rate of 2 mL/min. Purity was determined by integration of the UV (254 nm) and ELSD trace. The retention times (RT) are expressed in minutes.
Preparative LC-MS-purification was performed on the same instrument. Column: 50 X 20 mm YMC ODS-A with 5 µm particle size; Method: Linear gradient elution with 80% A to 100% B in 7 min and with a flow rate of 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

^{1}H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Chloroform (99.8%D) or dimethyl sulfoxide (99.8%D) were used as solvents. Tetramethylsilane (TMS) was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, h = heptet, dd = double doublet, dt = double triplet, dq = double quartet, tt = triplet of triplets, m = multiplet and b = broad singlet.

Reactions were run under inert atmosphere and dry conditions unless otherwise stated. Reactions carried out under microwave conditions were performed in a SmithSynthesizer from Personal Chemistry operating at 2450 MHz.

Preparation of Intermediates

1-bromo-2-(4-chloro-phenylsulfanyl)-5-(trifluoromethyl)-benzene (intermediate for **1a)**

To a stirred solution of tris(dibenzylidene)dipalladium(0) (Pd_2dba_3, 0.183 g, 0.2 mmol) and bis(2-diphenylphosphinophenyl)ether (DPEphos, 0.215 g, 0.2 mmol) in toluene (80 mL) was added 3-bromo-4-iodobenzotrifluoride (7.02 g, 20 mmol; prepared from 2-bromo-4-trifluoromethyl-phenylamine by diazotization according to the general procedure by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753), 4-chlorothiophenol (2.89 g, 20 mmol) and potassium *tert*-butoxide (2.46 g, 22 mmol) at room temperature (rt). The reaction mixture was stirred for 2.5 h at 100 °C and then cooled to room temperature (rt) and filtered through celite. The solvent was evaporated off and the crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate/heptane 2:8) to produce 4.53 g (81%) of 1-bromo-2-(4-chloro-phenylsulfanyl)-5-(trifluoromethyl)-benzene as an oil.

The following intermediates for **1b-1m** and **2a-2x** were prepared analogously:

1-Bromo-2-(4-methoxy-phenylsulfanyl)-benzene (intermediate for **1b**). Prepared from 4-methoxy-benzenethiol and 1-bromo-2-iodo-benzene.

1-Bromo-2-(2,4-dimethyl-phenylsulfanyl)-5-(trifluoromethyl)-benzene (intermediate for **1c**). Prepared from 2,4-dimethyl-benzenethiol and 2-bromo-1-iodo-4-trifluoromethyl-benzene.

1-Bromo-2-(4-chloro-phenylsulfanyl)-4-fluoro-benzene (intermediate for **1d**). Prepared from 4-chloro-benzenethiol and 1-bromo-4-fluoro-2-iodo-benzene.

1-Bromo-4-fluoro-2-(4-methoxy-phenylsulfanyl)-benzene (intermediate for **1e**). Prepared from 4-methoxy-benzenethiol and 1-bromo-4-fluoro-2-iodo-benzene.

1-Bromo-2-(4-methyl-phenylsulfanyl)-5-methyl-benzene (intermediate for **1f**). Prepared from 4-methyl-benzenethiol and 2-bromo-1-iodo-4-methyl-benzene.

1-Bromo-2-(2,4-dimethyl-phenylsulfanyl)-5-methyl-benzene (intermediate for **1g**) . Prepared from 2,4-dimethyl-benzenethiol and 2-bromo-1-iodo-4-methyl-benzene.

1-Bromo-2-(4-fluoro-2-methyl-phenylsulfanyl)-5-methyl-benzene (intermediate for **1h**). Prepared from 4-fluoro-1-iodo-2-methyl-benzene and 2-bromo-4-methyl-benzenethiol (prepared from 2-bromo-4-methyl-phenylamine by diazotization according to the procedure reported for the conversion of 3-toluidine to 3-thiocresol by Tarbell and Fukushima *J. Am. Chem. Soc.* **1946**, *68*, 1456-1460).

1-Bromo-2-(4-methoxy-phenylsulfanyl)-5-methyl-benzene (intermediate for **1i**) . Prepared from 4-methoxy-benzenethiol and 2-bromo-1-iodo-4-methyl-benzene.

1-Bromo-2-(4-chloro-2-methyl-phenylsulfanyl)-benzene (intermediate for **1j**). Prepared from 4-chloro-1-iodo-2-methyl-benzene and 2-bromo-benzenethiol.

1-Bromo-2-(4-chloro-2-fluoro-phenylsulfanyl)-benzene (intermediate for **1k**). Prepared from 4-chloro-2-fluoro-1-iodo-benzene and 2-bromo-benzenethiol.

1-Bromo-2-(2,4-dichloro-phenylsulfanyl)-benzene (intermediate for **1l**). Prepared from 2,4-dichloro-benzenethiol and 2-bromo-1-iodo-benzene.

1-Bromo-2-(2-chloro-4-methoxy-phenylsulfanyl)-benzene (intermediate for **1m**). Prepared from 2-bromo-benzenethiol and 2-chloro-1-iodo-4-methoxy-benzene (prepared from 4-amino-3-chloro-phenol by diazotization according to the general procedure by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753 followed by alkylation with methyl iodide according to the general procedure by Uozumi *et al. J. Org. Chem.* **1993**, *58*, 1945-1945)

1-Bromo-2-(4-chloro-phenylsulfanyl)-benzene (intermediate for **2a**). Prepared from 4-chloro-benzenethiol and 1-bromo-2-iodo-benzene.

2-Bromo-5-fluoro-1-(4-methoxy-phenylsulfanyl)-benzene (intermediate for **2b**). Prepared from 4-methoxy-benzenethiol and 2-bromo-4-fluoro-1-iodo-benzene

(prepared from 2-bromo-4-fluoro-phenylamine by diazotization according to the general procedure by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753)

1-Bromo-2-(4-chloro-phenylsulfanyl)-5-fluoro-benzene (intermediate for **2e**). Prepared from 4-chloro-benzenethiol and 2-bromo-4-fluoro-1-iodo-benzene.

1-Bromo-3-fluoro-2-(4-methoxy-phenylsulfanyl)-benzene (intermediate for **2d**). Prepared from 4-methoxy-benzenethiol and 1-bromo-3-fluoro-2-iodo-benzene (prepared from 2-bromo-6-fluoro-phenylamine by diazotization according to the general procedure by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753).

1,5-Dibromo-2-(2,4-dimethyl-phenylsulfanyl)-benzene (intermediate for **2e**). Prepared from 2,4-dimethyl-benzenethiol and 2,4-dibromo-1-iodo-benzene (prepared from 2,4-dibromo-phenylamine by diazotization according to the general procedure by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753).

1-Bromo-4-fluoro-2-(4-methyl-phenylsulfanyl)-benzene (intermediate for **2f**). Prepared from 4-methyl-benzenethiol and 1-bromo-4-fluoro-2-iodo-benzene.

1-Bromo-2-(4-chloro-phenylsulfanyl)-5-methyl-benzene (intermediate for **2g**). Prepared from 4-chloro-benzenethiol and 2-bromo-1-iodo-4-methyl-benzene.

1-Bromo-2-(4-methyl-phenylsulfanyl)-5-trifluoromethyl-benzene (intermediate for **2h**). Prepared from 4-methyl-benzenethiol and 3-bromo-4-iodo-benzotrifluoride.

1-Bromo-5-fluoro-2-(2,4-dimethyl-phenylsulfanyl)-benzene (intermediate for **2i**). Prepared from 2,4-dimethyl-benzenethiol and 2-bromo-4-fluoro-1-iodo-benzene.

1-Bromo-2-(4-fluoro-phenylsulfanyl)-5-fluoro-benzene (intermediate for **2j**). Prepared from 4-fluoro-benzenethiol and 2-bromo-4-fluoro-1-iodo-benzene.

1-Bromo-2-(2-chloro-4-fluoro-phenylsulfanyl)-5-fluoro-benzene (intermediate for **2k**). Prepared from 2-chloro-4-fluoro-benzenethiol and 2-bromo-4-fluoro-1-iodo-benzene.

1-Bromo-5-fluoro-2-(4-methyl-phenylsulfanyl)-benzene (intermediate for **2l**). Prepared from 4-methyl-benzenethiol and 2-bromo-4-fluoro-1-iodo-benzene.

1-Bromo-5-fluoro-2-(3-methoxy-phenylsulfanyl)-benzene (intermediate for **2m**). Prepared from 3-methoxy-benzenethiol and 2-bromo-4-fluoro-1-iodo-benzene.

1-Bromo-2-(2-chloro-4-methyl-phenylsulfanyl)-5-fluoro-benzene (intermediate for **2n**). Prepared from 2-chloro-4-methyl-benzenethiol and 2-bromo-4-fluoro-1-iodo-benzene.

1-Bromo-2-(2-chloro-4-methoxy-phenylsulfanyl)-5-fluoro-benzene (intermediate for **2o**). Prepared from 2-chloro-1-iodo-4-methoxy-benzene and 2-bromo-4-fluoro-benzenethiol (prepared from 2-bromo-4-fluoro-phenylamine by diazotization according to the procedure reported for the conversion of 3-toluidine to 3-thiocresol by Tarbell and Fukushima *J. Am. Chem. Soc.* **1946**, *68*, 1456-1460).

1-Bromo-2-(4-chloro-2-fluoro-phenylsulfanyl)-5-fluoro-benzene (intermediate for **2p**). Prepared from 4-chloro-2-fluoro-1-iodo-benzene and 2-bromo-4-fluoro-benzenethiol.

1-Bromo-2-(2-fluoro-4-methyl-phenylsulfanyl)-5-fluoro-benzene (intermediate for **2q**). Prepared from 2-fluoro-1-iodo-4-methyl-benzene and 2-bromo-4-fluoro-benzenethiol.

1-Bromo-2-(2-chloro-phenylsulfanyl)-5-fluoro-benzene (intermediate for **2r**). Prepared from 2-chloro-benzenethiol and 2-bromo-4-fluoro-1-iodo-benzene.

1-Bromo-2-(2,4-dichloro-phenylsulfanyl)-5-fluoro-benzene (intermediate for **2s**). Prepared from 2,4-dichloro-benzenethiol and 2-bromo-4-fluoro-1-iodo-benzene.

1-Bromo-2-(2,4-difluoro-phenylsulfanyl)-5-fluoro-benzene (intermediate for **2t**). Prepared from 2,4-difluoro-benzenethiol and 2-bromo-4-fluoro-1-iodo-benzene.

1-Bromo-2-(2,4-dimethyl-phenylsulfanyl)-3-fluoro-benzene (intermediate for **2u**). Prepared from 2,4-dimethyl-benzenethiol and 1-bromo-3-fluoro-2-iodo-benzene.

1-Bromo-5-fluoro-2-(phenylsulfanyl)-benzene (intermediate for **2v**). Prepared from benzenethiol and 2-bromo-4-fluoro-1-iodo-benzene.

1-Bromo-2-(4-bromo-2-fluoro-phenylsulfanyl)-5-fluoro-benzene (intermediate for **2x**). Prepared from 4-bromo-2-fluoro-1-iodo-benzene and 2-bromo-4-fluoro-benzenethiol.

4-(5-Fluoro-2-mercapto-phenyl)-4-hydroxy-piperidine-1-carboxylic acid tert-*butyl ester (intermediate for **2a1-2a6**)*

To a solution of 2-bromo-4-fluoro-thiophenol (6.0 g, 28.9 mmol) in dry tetrahydrofuran (THF, 25 mL) at –78°C was slowly added methyl lithium (1M in cumene/THF, 28.9 mL, 28.9 mmol). After 30 min at –78 °C, *tert*-butyl lithium (1.7 M in THF, 39.9mL, 63.8 mmol) was added and the reaction mixture was stirred 30 min at –78 °C. A solution of 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (5.77 g, 28.9 mmol) in THF (20 mL) was added and the reaction mixture was allowed to warm to rt and stirred overnight. Water (50 mL) and ethyl acetate (25 mL) were added, and organic phase was discarded. The aqueous phase was extracted with ethyl acetate (50 mL) and saturated aqueous ammonium chloride (25 mL). The organic phase was washed with saturated aqueous ammonium chloride (25 mL) and dried over magnesium sulfate, and evaporated to afford the crude product. The crude product was purified by flash chromatography on silica gel (eluent: An increasing amount (0-20%) of ethyl acetate in heptane). Yield: 4.67 g (49%).

*4-(2-Tri-*iso*-propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid* tert-*butyl ester (intermediate for **3a1-3a6**)*

To a 10 mL microwave vial was added 4-(2-hydroxy-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (0.30 g, 1.08 mmol), *N*-phenyl-bis(trifluoromethanesulfoneimide) (393 mg, 1.1 mmol), and potassium carbonate (448 mg, 3.25 mmol). THF (2.2 mL)

was added and the vial was closed with a septum. The mixture was heated under microwave conditions at 120°C for 10 min. The reaction mixture was cooled to rt and diluted with diethyl ether (10 mL). The mixture was filtered through celite, the solvent was evaporated off and the crude product was purified by chromatography on silica gel (eluent: An increasing amount (0-100%) of ethyl acetate in heptane) to produce 349 mg of 4-(2-trifluoromethanesulfonyloxy-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester. Some of this material (92 mg, 0.22 mmol) and tri-(*iso*-propyl)-silanethiol (59 mg, 0.31 mmol) was dissolved in dry toluene (1.1 mL) and added to palladium(II) acetate (5 mg, 0.022 mmol), (S)-2,2'-bis-(di-*p*-tolyl-phosphanyl)-[1,1']binaphthalenyl (S-(-)-Tol-BINAP,16 mg, 0.024 mmol) and sodium *tert*-butoxide (30 mg, 0.31 mmol) placed in a 10 mL microwave vial. THF (2.2 mL) was added and the vial was closed with a septum. The mixture was heated under microwave conditions at 120°C for 30 min. The reaction mixture was cooled to rt and the solvent was evaporated off. The crude product was purified by flash chromatography on silica gel (eluent: An increasing amount (0-100%) of ethyl acetate in heptane). Yield of 4-(2-tri-*iso*-propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester: 64 mg (65%).

4-(5-Methyl-2-tri-iso-*propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid* tert-*butyl ester (intermediate for **3b1-3b12**)* was prepared in a similar way from 4-(2-hydroxy-5-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester. This compound was prepared from 2-bromo-4-methyl-phenol by the following procedure: A mixture of 2-bromo-4-methyl-phenol (1.12 g, 6.0 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (1.86 g, 6.0 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (0.245 g, 0.3 mmol), and potassium carbonate (2.48 g, 18.0 mmol) was suspended in 1,2-dimethoxy-ethane (DME, 23 mL) and water (7 mL). The suspension was stirred overnight at 90°C, cooled to RT, and then quenched at 5°C by adding aqueous hydrochloric acid (2M, 18 mL). Diethyl ether (18 mL) was added, the phases were separated and the aqueous phase was extracted with diethyl ether (2 x 18 mL) The combined organic phases were washed with saturated aqueous sodium chloride (30 mL), and dried over magnesium sulfate, and evaporated. The crude product was purified by chromatography on silica gel (eluent: An increasing amount

(0-100%) of ethyl acetate in heptane). Yield: 1.03 g (59%) of the intermediate 4-(2-hydroxy-5-methyl-phenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester. This material was dissolved in ethanol (35 mL), 20% Pd/C (0.1 g) was added, and the mixture was treated with hydrogen gas (3 bar) on a Parr shaker apparatus overnight. The mixture was filtered through celite and the solvent was evaporated off to produce 4-(2-hydroxy-5-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester. Yield: 0.91 g (91%).

*4-(5-Methoxy-2-*tri-*iso-propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid* tert-*butyl ester* (intermediate for ***3c1-3c4***) was prepared in a similar way from 4-(2-hydroxy-5-methoxy-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester. This compound was prepared from 2-bromo-4-methoxy-phenol (prepared by bromination from 4-methoxy-phenol according to the procedure by Carreno *et al. Synlett* **1997**, 1241-1242) was coupled to 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester, and the product was reduced with Pd/C and hydrogen gas as described for 4-(2-hydroxy-5-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester.

*4-(2-Fluoro-6-tri-*iso-*propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid* tert-*butyl ester* (intermediate for ***3d1-3d27***). A solution of 1-fluoro-3-methoxy-benzene (10.0g, 79.3 mmol) in dry THF (100 mL) was treated with *n*-butyl lithium (1.6M in hexane, 49.8 mL, 79.3 mmol) at –78 °C for five hours. A solution of 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (15.8 g, 79.3 mmol) in THF (50 mL) was added at a rate so that the temperature was maintained below –65°C, and the reaction mixture was allowed to warm to rt and stirred overnight. Saturated aqueous ammonium chloride (50 mL) followed by ethyl acetate (10 mL) was added. The organic layer was washed with saturated aqueous ammonium chloride (50 mL), dried over magnesium sulfate, and evaporated *in vacuo* to afford the crude product. Purification by chromatography over silica gel (eluent: ethyl acetate/heptane 1:1) provided 7.80 g (31%) of 4-(2-fluoro-6-methoxy-phenyl)-4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester. A solution of this compound in acetic acid (70 mL) was treated with concentrated aqueous hydrochloric acid (30 mL) at reflux overnight. The volatiles were removed *in vacuo*, and the residue was partitioned between

methylene chloride (100 mL) and a mixture of saturated aqueous sodium bicarbonate (100 mL) and aqueous sodium hydroxide (10%, to adjust pH to 11). The organic layer was dried over magnesium sulfate and the volatiles were removed *in vacuo*. The residue was refluxed overnight in a mixture of 33% hydrogen bromide in acetic acid (10 mL) and concentrated aqueous hydrobromic acid (20 mL). Approximately 15 mL of the solvent was removed *in vacuo* and the residue was cooled on an icebath for 3 h to precipitate 4.10 g (59% overall) of 4-(5-fluoro-2-methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine as the hydrobromic acid salt. A slurry of this compound (4.10 g, 14.2 mmol) in 1,2-dichloro-ethane (100 mL) and triethyl amine (2.3 mL) is stirred at rt for 30 min before Boc_2O (2.78 g, 14.0 mmol) was added. After stirring overnight, the precipitate was filtered off, and the filtrate is washed with saturated aqueous ammonium chloride (50 mL) and dried over magnesium sulfate. The volatiles were removed *in vacuo* to yield 1.02 g (23%) of 4-(2-fluoro-6-hydroxy-phenyl)- 1,2,3,6-tetrahydro-pyridine-1-carboxylic acid *tert*-butyl ester. This material was dissolved in a mixture of ethyl acetate (10 mL) and ethanol (40 mL) and treated overnight with 5% Pd/C (0.1 g) and hydrogen gas (3 bar) using a Parr shaker apparatus. The catalyst was removed by filtration, and the volatiles were removed *in vacuo*. The residue (1.0 g) was suspended in 1,2-dichloro-ethane (20 mL) and treated with ethyl-di-*iso*-propyl-amine (0.53 g, 4.1 mmol) at 0 °C for 30 min before 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonyl fluoride (1.12 g, 3.7 mmol) was added and stirring was continued overnight at rt. The precipitate was filtered off, and the filtrate was washed with water (20 mL), dried over magnesium sulfate, and evaporated to afford the crude product. Purification by chromatography over silica gel (eluent: ethyl acetate/heptane 1:4) provided 1.27 g (65% over two steps) of 4-[2-fluoro-6-(nonafluorobutane-1-sulfonyloxy)-phenyl]-piperidine-1-carboxylic acid *tert*-butyl ester. A mixture of this compound (1.27 g, 2.2 mmol) and sodium *tert*-butoxide (0.27 g, 2.9 mmol) in dry toluene (25 mL) was added to a solution of Pd_2dba_3 (0.10 g, 0.11 mmol) and DPEphos (0.12 g, 0.22 mmol) in dry toluene (25 mL). Tri-*iso*-propyl-silanethiol (0.42 g, 2.2 mmol) was added, and the mixture was stirred for 5 h at 100°C. After cooling to rt, the crude mixture was washed with water (50 mL), dried over magnesium sulfate, and the volatiles were removed *in vacuo*. The residue was pyrified by chromatography over silica gel (eluent: ethyl acetate/heptane 1:4) to yield 0.8 g (78%) of 4-(2-fluoro-6-tri-*iso*-propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester.

*4-(5-Fluoro-2-*tri-*iso-propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid* tert-*butyl ester* (intermediate for ***3e1-3e10***).

A mixture of 2-bromo-4-fluoro-1-methoxy-benzene (36.2 g, 176.7 mmol) and dry THF (25 mL) was added to a cooled solution of *n*-butyl lithium (2.1 M in hexane, 101 mL, 212.1 mmol) in dry THF (100 mL) at at rate so that the temperature was maintained below –40 °C. The mixture was stirred for 30 min at –78 °C before 4-oxo-piperidine-1-carboxylic acid ethyl ester (30.4 g, 176.7 mmol) was added at a rate so that the temperature was maintained below –50 °C. The resulting mixture was allowed to warm to rt and stirring was continued overnight. Water (100 mL) and ethyl acetate (100 mL) was added. The organic layer was washed with saturated aqueous ammonium chloride (100 mL), dried over magnesium sulfate, and evaporated *in vacuo* to afford 52.3 g (>95%.) of 4-(5-fluoro-2-methoxy-phenyl)-4-hydroxy-piperidine-1-carboxylic acid ethyl ester, which was sufficiently pure for the next step. This material was dissolved in triethyl-silane (100 mL) and TFA (200 mL) and stirred at rt for 3 days. The volatiles were removed *in vacuo* and the residue was purified by chromatography on silica gel (eluent: ethyl acetate/heptane 1:3) to afford 44.4 g (ca. 90%) of 4-(5-fluoro-2-methoxy-phenyl)-piperidine-1-carboxylic acid ethyl ester. This material was refluxed overnight in a mixture of 33% hydrogen bromide in acetic acid (75 mL) and concentrated aqueous hydrobromic acid (75 mL). The crude mixture was cooled on an icebath, and 18.9 g (43%) of 4-fluoro-2-piperidin-4-yl-phenol as the hydrobromic acid salt. A slurry of this compound (23.9 g, 86.5 mmol) in dichloromethane (200 mL) was treated with triethyl amine (13.2 mL, 95.2 mmol) for 1 h before Boc_2O (18.9 g, 86.5 mmol) was added and stirring was continued for 30 min. The crude mixture was washed with saturated aqueous ammonium chloride (50 mL) and water (25 mL). The organic layer was dried over magnesium sulfate and the volatiles were removed *in vacuo*. The residue crystallized to yield 14.2 g (55%) of 4-(5-fluoro-2-hydroxy-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester. This compound was transformed into 4-(5-fluoro-2-tri-*iso*-propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester in a similar way as described for 4-(2-fluoro-6-tri-*iso*-propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester.

4-(4-Fluoro-2-tri-*iso-propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid* tert-*butyl ester* (intermediate for ***3f1-3f13***).

Using the procedure described for 4-(2-hydroxy-5-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester, 2-bromo-5-fluoro-phenol was converted into 4-(4-fluoro-2-hydroxy-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester. This compound was transformed into 4-(4-fluoro-2-triisopropylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester under conditions described for 4-(2-fluoro-6-tri-*iso*-propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester.

4-Hydroxy-4-(2-mercapto-phenyl)-piperidine-1-carboxylic acid tert-*butyl ester (intermediate for **4a**)*

This intermediate was prepared from 2-bromo-benzenethiol and 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester in a similar way as described for 4-(5-fluoro-2-mercapto-phenyl)-4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester.

Preparation of further intermediates

1-tert-*Butoxycarbonyl-4-[2-(4-chlorophenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine-4-ol (intermediate for **1a**)*

A solution of *n*-butyl lithium (2.5 M in hexane, 6.5 mL, 16.2 mmol) was slowly added to a stirred solution of 1-bromo-2-(4-chlorophenylsulfanyl)-5-(trifluoromethyl)benzene (5.96 g, 16.2 mmol) in dry THF (40 mL) under argon at –78 °C. The solution was stirred for 10 min before 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (3.23 g, 16.2 mmol) was added in one portion. The solution was allowed to warm to rt and then stirred overnight. Saturated aqueous ammonium chloride (80 mL) was added and the solution was extracted with ethyl acetate (80 mL). The organic phase was washed with saturated aqueous sodium chloride (50 mL), dried over magnesium sulfate and the solvent was evaporated off. The crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate/heptane 2:8) to produce the target compound as a white foam, yield: 4.53 g (57%).

The following intermediates for **1b-1m** and **2a-2x** were prepared analogously from the corresponding previously described intermediates:

1-tert-*Butoxycarbonyl-4-[2-(4-methoxy-phenylsulfanyl)-phenyl]-piperidine-4-ol (intermediate for **1b**)* .

1-tert-*Butoxycarbonyl-4-[2-(2,4-dimethyl-phenylsulfanyl)-5-(trifluoromethyl-phenyl]-piperidine-4-ol (intermediate for **1c**).*

1-tert-*Butoxycarbonyl-4-[2-(4-chloro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine-4-ol (intermediate for **1d**).*

1-tert-*Butoxycarbonyl-4-[2-(4-methoxy-phenylsulfanyl)-4-fluoro-phenyl]-piperidine-4-ol (intermediate for **1e**).*

1-tert-*Butoxycarbonyl-4-[2-(4-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine-4-ol (intermediate for **1f**).*

1-tert-*Butoxycarbonyl-4-[2-(2,4-dimethyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine-4-ol (intermediate for **1g**).*

1-tert-*Butoxycarbonyl-4-[2-(4-fluoro-2-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine-4-ol (intermediate for **1h**).*

1-tert-*Butoxycarbonyl-4-[2-(4-methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine-4-ol (intermediate for **1i**).*

1-tert-*Butoxycarbonyl-4-[2-(4-chloro-2-methyl-phenylsulfanyl)-phenyl]-piperidine-4-ol (intermediate for **1j**)*

1-tert-*Butoxycarbonyl-4-[2-(4-chloro-2-fluoro-phenylsulfanyl)-phenyl]-piperidine-4-ol (intermediate for **1k**)*

1-tert-*Butoxycarbonyl-4-[2-(2,4-dichloro-phenylsulfanyl)-phenyl]-piperidine-4-ol (intermediate for **1l**)*

1-tert-*Butoxycarbonyl-4-[2-(2-chloro-4-methoxy-phenylsulfanyl)-phenyl]-piperidine-4-ol (intermediate for **1m**)*

1-tert-*Butoxycarbonyl-4-[2-(4-chloro-phenylsulfanyl)-phenyl]-piperidine-4-ol (intermediate for **2a**).*

1-tert-*Butoxycarbonyl-4-[2-(4-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2b**).*

1-tert-*Butoxycarbonyl-4-[2-(4-chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2c**).*

1-tert-*Butoxycarbonyl-4-[2-(4-methoxy-phenylsulfanyl)-3-fluoro-phenyl]-piperidine-4-ol (intermediate for **2d**)*

1-tert-*Butoxycarbonyl-4-[2-(2,4-dimethyl-phenylsulfanyl)-5-bromo-phenyl]-piperidine-4-ol (intermediate for **2e**)*

1-tert-*Butoxycarbonyl-4-[2-(4-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine-4-ol (intermediate for **2f**)*

1-tert-*Butoxycarbonyl-4-[2-(4-chloro-phenylsulfanyl)-5-methyl-phenyl]-piperidine-4-ol (intermediate for **2g**)*

1-tert-*Butoxycarbonyl-4-[2-(4-methyl-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine-4-ol (intermediate for **2h**)*

1-tert-*Butoxycarbonyl-4-[2-(2,4-dimethyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2i**)*

1-tert-*Butoxycarbonyl-4-[2-(4-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2j**)*

1-tert-*Butoxycarbonyl-4-[2-(2-chloro-4-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2k**)*

1-tert-*Butoxycarbonyl-4-[2-(4-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2l**)*

1-tert-*Butoxycarbonyl-4-[2-(3-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2m**)*

1-tert-*Butoxycarbonyl-4-[2-(2-chloro-4-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2n**)*

1-tert-*Butoxycarbonyl-4-[2-(2-chloro-4-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2o**)*

1-tert-*Butoxycarbonyl-4-[2-(4-chloro-2-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2p**)*

1-tert-*Butoxycarbonyl-4-[2-(2-fluoro-4-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2q**)*

1-tert-*Butoxycarbonyl-4-[2-(2-chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2r**)*

1-tert-*Butoxycarbonyl-4-[2-(2,4-dichloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2s**).*

1-tert-*Butoxycarbonyl-4-[2-(2,4-difluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2t**).*

1-tert-*Butoxycarbonyl-4-[2-(2,4-dimethyl-phenylsulfanyl)-3-fluoro-phenyl]-piperidine-4-ol (intermediate for **2u**).*

1-tert-*Butoxycarbonyl-4-[2-(phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2v**).*

1-tert-*Butoxycarbonyl-4-[2-(4-bromo-2-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2x**).*

Further intermediates for **2a1-2a6** were prepared from 4-hydroxy-4-(2-mercapto-5-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester, and appropriately substituted aryliodides as detailed below by the palladium-catalysed coupling procedure described for 1-bromo-2-(4-chloro-phenylsulfanyl)-5-(trifluoromethyl)-benzene.

1-tert-*Butoxycarbonyl-4-[2-(3-chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2a1**)*. Prepared from 4-hydroxy-4-(2-mercapto-5-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester and 1-chloro-3-iodo-benzene.

1-tert-*Butoxycarbonyl-4-[2-(3-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2a2**)*. Prepared from 4-hydroxy-4-(2-mercapto-5-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester and 1-fluoro-3-iodo-benzene.

1-tert-*Butoxycarbonyl-4-[2-(2-fluoro-4-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2a3**)*. Prepared from 4-hydroxy-4-(2-mercapto-5-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester and 2-fluoro-1-iodo-4-methoxy-benzene (prepared from 3-fluoro-4-nitro-phenol by reduction to 4-amino-3-fluoro-phenol as reported by Hogdson and Nicholson *J. Chem. Soc.* **1941**, 645-646 followed by diazotization according to the general procedure by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753 followed by alkylation with methyl iodide according to the general procedure by Uozumi *et al. J. Org. Chem.* **1993**, *58*, 1945-1945).

1-tert-*Butoxycarbonyl-4-[2-(4-methoxy-2-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2a4**).* Prepared from 4-hydroxy-4-(2-mercapto-5-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester and 1-iodo-4-methoxy-2-methyl-benzene (prepared from 4-methoxy-2-methyl-phenylamine by diazotization according to the general procedure by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753).

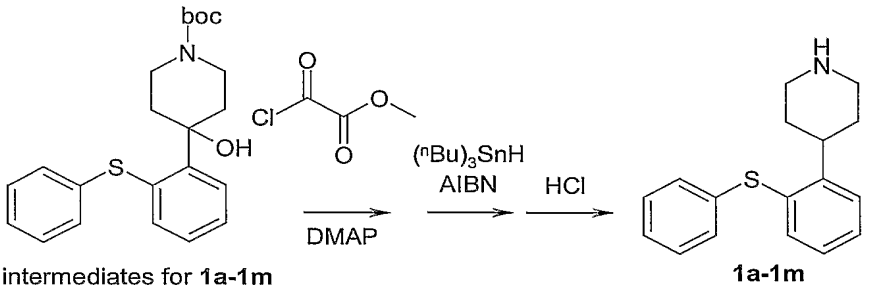
1-tert-*Butoxycarbonyl-4-[2-(2-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2a5**).* Prepared from 4-hydroxy-4-(2-mercapto-5-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester and 1-iodo-2-methyl-benzene.

1-tert-*Butoxycarbonyl-4-[2-(2-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2a6**).* Prepared from 4-hydroxy-4-(2-mercapto-5-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester and 2-fluoro-1-iodo-benzene.

1-tert-*Butoxycarbonyl-4-[2-(4-methoxycarbonyl-phenylsulfanyl)-phenyl]-piperidine-4-ol (intermediate for **4a**)* was prepared from 4-hydroxy-4-(2-mercapto-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester, and 4-iodo-benzoic acid methyl ester by the palladium-catalysed coupling procedure described for 1-bromo-2-(4-chloro-phenylsulfanyl)-5-(trifluoromethyl)-benzene.

Compounds of the invention:

Method A:



intermediates for **1a-1m** **1a-1m**

Example 1

1a, *4-[2-(4-Chloro-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine fumaric acid salt*

Chloro-oxo-acetic acid methyl ester (1.37 g, 11.2 mmol) was added to a stirred solution of 1-*tert*-butoxycarbonyl-4-[2-(4-chloro-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine-4-ol (0.98 g, 2.0 mmol) and dimethyl-pyridin-4-yl-amine (DMAP, 0.44 g, 3.6 mmol) in dry acetonitrile (6.4 mL) at 0 °C under argon. The reaction mixture was allowed to reach room temperature and then stirred overnight. Ethyl acetate (40 mL) was added and the precipitated salts were removed by filtration through celite. The organic phase was washed with saturated aqueous sodium bicarbonate (40 mL), saturated aqueous sodium chloride (40 mL), and dried over magnesium sulfate. The volatiles were evaporated off, and the crude material was dried *in vacuo*. This material was dissolved in dry toluene (13 mL) under argon. Tri-*n*-butyl tin hydride (0.81 g, 3.0 mmol) and 2-[(cyano-dimethyl-methyl)-azo]-2-methyl-propionitrile (AIBN, 82 mg, 0.5 mmol) were added. The solution was stirred under argon at 90 °C for 3.5 h. The solvent was evaporated, and the crude material was purified by chromatography on silica gel (eluent: ethyl acetate/ heptane 1:9) to produce 4-[2-(4-chloro-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine-1-carboxylic acid *tert*-butyl ester as a clear oil (0.77 g, 82%). This oil was dissolved in methanol (8 mL) and hydrogen chloride in diethyl ether (2M, 8 mL) was added at 0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated off and ethyl acetate (25 mL) was added. The organic phase was extracted with aqueous sodium hydroxide (2M, 8 mL) and washed with saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate, and the solvent was evaporated off. This material (588 mg) was dissolved in ethyl acetate (2.2 mL) and fumaric acid (183 mg, 1.58 mmol) dissolved in hot ethanol (96%, 4.4 mL) was added. The target compound was collected as a white solid. LC/MS (m/z) 372.1 (MH^+); RT = 2.54; purity (UV, ELSD): 97%, 100%; yield: 0.187 g (19%).

The following compunds of the invention **1b-1m** were prepared analogously from the corresponding previously described intermediates:

1b, *4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-piperidine oxalic acid salt* was collected as a white solid. LC/MS (m/z) 299.9 (MH^+); RT = 2.04; purity (UV, ELSD): 95%, 97%; yield: 0.090 g (10%).

1c, *4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine oxalic acid salt* was collected as a white solid. LC/MS (m/z) 366.2 (MH^+); RT = 2.45; purity (UV, ELSD): 97%, 99%; yield: 0.61 g (45%).

1d, *4-[2-(4-Chloro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine oxalic acid salt* was collected as a white solid. LC/MS (m/z) 322.1 (MH^+); RT = 2.33; purity (UV, ELSD): 83%, 97%; yield: 0.385 g (51%).

1e, *4-[2-(4-Methoxy-phenylsulfanyl)-4-fluoro-phenyl]-piperidine hydrochloric acid salt* was collected as a white solid. LC/MS (m/z) 318.1 (MH^+); RT = 2.12; purity (UV, ELSD): 96%, 99%; yield: 0.308 g (30%).

1f, *4-[2-(4-Methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine oxalic acid salt* was collected as a white solid. LC/MS (m/z) 298.2 (MH^+); RT = 2.29; purity (UV, ELSD): 98%, 99%; yield: 0.233 g (33%).

1g, *4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine oxalic acid salt* was collected as a white solid. LC/MS (m/z) 312.0 (MH^+); RT = 2.41; purity (UV, ELSD): 98%, 100%; yield: 0.233 g (33%).

1h, *4-[2-(4-Fluoro-2-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine oxalic acid salt* was isolated as a white solid. LC/MS (m/z) 316.0 (MH^+); RT = 2.33; purity (UV, ELSD): 96%, 100%; yield: 0.336 g (34%).

1i, *4-[2-(4-Methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine oxalic acid salt* was collected as a white solid. LC/MS (m/z) 313.8 (MH^+); RT = 2.16; purity (UV, ELSD): 96%, 99%; yield: 0.375 g (34%).

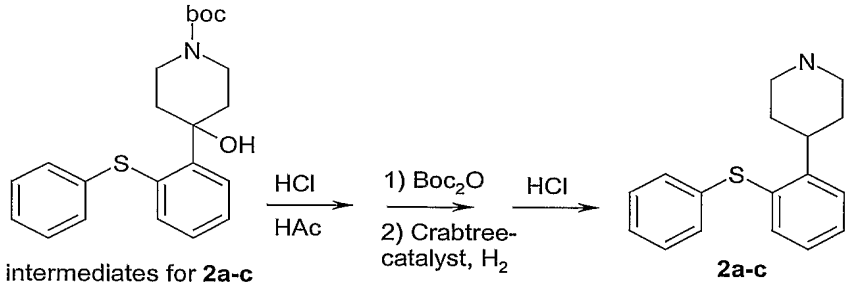
1j, *4-[2-(4-Chloro-2-methyl-phenylsulfanyl)-phenyl]-piperidine trifluoro-acetic acid salt* was collected as a clear oil. LC/TOF (m/z) 318.0 (MH^+); RT = 2.36; purity (UV, ELSD): 99.7%, 99.0%.

1k, *4-[2-(4-Chloro-2-fluoro-phenylsulfanyl)-phenyl]-piperidine trifluoro-acetic acid salt* was collected as a clear oil. LC/MS (m/z) 322.0 (MH^+); RT = 2.27; purity (UV, ELSD): 94.6%, 99.7%.

1l, *4-[2-(2,4-Dichloro-phenylsulfanyl)-phenyl]-piperidine trifluoro-acetic acid salt* was collected as a clear oil. LC/MS (m/z) 337.9 (MH^+); RT = 2.37; purity (UV, ELSD): 94.9%, 99.6%.

1m, *4-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-phenyl]-piperidine trifluoro-acetic acid salt* was collected as a clear oil. LC/MS (m/z) 334.0 (MH^+); RT = 2.23; purity (UV, ELSD): 95.9, 99.9.

Method B:



intermediates for **2a-c** **2a-c**

2a, *4-[2-(4-Chloro-phenylsulfanyl)-phenyl- piperidine oxalic acid salt*

Concentrated aqueous hydrochloric acid (150 mL) was added to a stirred solution of 1-*tert*-butoxycarbonyl-4-[2-(4-chloro-phenylsulfanyl)-phenyl]-piperidine-4-ol (12.13 g, 28.9 mmol) in acetic acid (450 mL). The solution was refluxed overnight, cooled to room temperature and then stirred on an ice bath. A saturated aqueous solution of sodium hydroxide (250 mL) was slowly added and the unclear solution was extracted with ethyl acetate (3 x 450 mL). The combined organic phases were washed with

saturated aqueous sodium chloride (450 mL), dried over magnesium sulfate and the solvents evaporated off. The crude material (8.02 g) was dissolved in THF (195 mL) and di-*tert*-butyl dicarbonate (Boc_2O, 6.96 g, 31.9 mmol) and triethyl amine (5 mL) were added. The mixture was stirred overnight and then quenched by addition of saturated aqueous ammonium chloride (200 mL). The organic phase was dried over magnesium sulfate, and the solvent was evaporated off. The crude material was purified by chromatography on silica gel (eluent: An increasing amount of ethyl acetate (0-20%) in heptane) to produce 4-[2-(4-chloro-phenylsulfanyl)-phenyl]-piperidine-1-carboxylic acid *tert*-butyl ester as a white solid (5.63 g). This material was dissolved in methylene chloride (130 mL). Hydrogen gas (3 bar) was bubbled through the solution using a Parr shaker apparatus and (1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)(hexafluorophosphine) iridium(I) (Crabtree's catalyst, 0.495 g, 1.40 mmol) was added and the hydrogenation was allowed to continue overnight. The catalyst was filtered off and the crude product was purified by chromatography on silica gel (eluent: An increasing amount of ethyl acetate (0-20%) in heptane) to produce 4-[2-(4-chloro-phenylsulfanyl)-phenyl]-piperidine-1-carboxylic acid *tert*-butyl ester (5.37 g). This material was dissolved in methanol (70 mL) and hydrogen chloride in diethyl ether (2M, 67 mL, 133 mmol) was added and the reaction mixture was stirred overnight. The solvent was evaporated off, and aqueous sodium hydroxide (2M, 200 mL), and ethyl acetate (400 mL) were added. The phases were separated, and the aqueous phase was extracted with ethyl acetate (400 mL). The combined organic phases were washed with saturated aqueous sodium chloride (300 mL), dried over magnesium sulfate, and the solvent was evaporated off. The residue was purified by chromatography on silica gel (eluent: An increasing amount of ethanol (0-25%) in ethyl acetate containing 5% triethyl-amine) to produce 4-[2-(4-chloro-phenylsulfanyl)-phenyl]-piperidine (1.63 g). This material was dissolved in THF at 50°C and a solution of oxalic acid (0.48 g) in THF was slowly added. 4-[2-(4-chloro-phenylsulfanyl)-phenyl]-piperidine oxalic acid salt was collected as a white solid. LC/MS (m/z) 304.0 (MH^+); RT = 2.29; purity (UV, ELSD): 96%, 96%; yield: 1.86 g (15%).

The following compounds of the invention **2b-2x** and **2a1-2a6** were prepared analogously from the corresponding previously described intermediates:

2b, *4-[2-(4-Methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine oxalic acid salt* was collected as a white solid. LC/MS (m/z) 318.1 (MH^+); RT = 2.16; purity (UV, ELSD): 91%, 98%.

2c, *4-[2-(4-Chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine oxalic acid salt* was collected as a white solid. LC/MS (m/z) 321.9 (MH^+); RT = 2.33; purity (UV, ELSD): 94%, 96%; yield: 0.241 g.

2d, *4-[2-(4-Methoxy-phenylsulfanyl)-3-fluoro-phenyl]-piperidine oxalic acid salt* was collected as a white solid. LC/MS (m/z) 318.1 (MH^+); RT = 2.12; purity (UV, ELSD): 98.6%, 98.5%.

2e, *4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-bromo-phenyl]-piperidine fumaric acid salt* was collected as a white solid. LC/MS (m/z) 378.0 (MH^+); RT = 2.50; purity (UV, ELSD): 99.3%, 98.5%.

2f, *4-[2-(4-Methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was collected as a clear oil. LC/MS (m/z) 302.1 (MH^+); RT = 2.12; purity (UV, ELSD): 73.3%, 97.9%.

2g, *4-[2-(4-Chloro-phenylsulfanyl)-5-methyl-phenyl]-piperidine trifluoro-acetic acid salt* was collected as a clear oil. LC/MS (m/z) 317.0 (MH^+); RT = 2.41; purity (UV, ELSD): 94.9%, 99.8%.

2h, *4-[2-(4-Methyl-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine trifluoro-acetic acid salt* was collected as a clear oil. LC/MS (m/z) 352.2 (MH^+); RT = 2.49; purity (UV, ELSD): 95.0%, 99.8%.

2i, *4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine oxalic acid salt* was collected as a white solid. LC/MS (m/z) 316.1 (MH^+); RT = 2.38; purity (UV, ELSD): 95.1%, 100%.

2j, *4-[2-(4-Fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine oxalic acid salt* was collected as a white solid. LC/MS (m/z) 306.0 (MH^+); RT = 2.10; purity (UV, ELSD): 88.1%, 97.6%.

2k, *4-[2-(2-Chloro-4-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine oxalic acid salt* was collected as a white solid. LC/MS (m/z) 340.0 (MH^+); RT = 2.20; purity (UV, ELSD): 95.1%, 100%.

2l, *4-[2-(4-Methyl-4-phenylsulfanyl)-5-fluoro-phenyl]-piperidine fumaric acid salt* was collected as a white solid. LC/MS (m/z) 302.0 (MH^+); RT = 2.26; purity (UV, ELSD): 96%, 99.7%.

2m, *4-[2-(3-Methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine oxalic acid salt* was collected as a white solid. LC/MS (m/z) 318.0 (MH^+); RT = 2.17; purity (UV, ELSD): 91.1%, 97.1%.

2n, *4-[2-(2-Chloro-4-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine fumaric acid salt* was collected as a white solid. LC/MS (m/z) 335.9 (MH^+); RT = 2.24; purity (UV, ELSD): 95.8%, 99.6%.

2o, *4-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine fumaric acid salt* was collected as a white solid. LC/MS (m/z) 352.2 (MH^+); RT = 2.27; purity (UV, ELSD): 95.8%, 97.2%.

2p, *4-[2-(4-Chloro-2-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine fumaric acid salt* was collected as a white solid. LC/MS (m/z) 340.0 (MH^+); RT = 2.25; purity (UV, ELSD): 97.4%, 99.9%.

2q, *4-[2-(2-Fluoro-4-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine fumaric acid salt* was collected as a white solid. LC/MS (m/z) 320.0 (MH^+); RT = 2.22; purity (UV, ELSD): 92.7%, 97.1%.

2r, *4-[2-(2-Chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine hydrobromic acid salt* was collected as a clear oil. LC/MS (m/z) 321.9 (MH^+); RT = 2.14 min; purity (UV, ELSD): 72.0%, 96.6%.

2s, *4-[2-(2,4-Dichloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine fumaric acid salt* was collected as a white solid. LC/MS (m/z) 358.0 (MH^+); RT = 2.34; purity (UV, ELSD): 97%, 99%.

2t, *4-[2-(2,4-Difluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine fumaric acid salt* was collected as a white solid. LC/MS (m/z) 324.0 (MH^+); RT = 2.11; purity (UV, ELSD): 97.0%, 100%.

2u, *4-[2-(2,4-Dimethyl-phenylsulfanyl)-3-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was collected as a clear oil. LC/MS (m/z) 314.0 (MH^+); RT = 2.33; purity (UV, ELSD): 85.3%, 98.5%.

2v, *4-[2-(Phenylsulfanyl)-5-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was collected as a clear oil. LC/MS (m/z) 288.0 (MH^+); RT = 2.06; purity (UV, ELSD): 98.6%, 99.4%.

2x, *4-[2-(4-Bromo-2-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was collected as a clear oil. LC/MS (m/z) 386.0 (MH^+); RT = 2.16; purity (UV, ELSD): 96.7%, 99.3%.

2a1, *4-[2-(3-Chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine oxalic acid salt* was collected as a white solid. LC/MS (m/z) 322.0 (MH^+); RT = 2.22; purity (UV, ELSD): 95.4%, 89%.

2a2, *4-[2-(3-Fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine oxalic acid salt* was collected as a clear oil. LC/MS (m/z) 306.0 (MH^+); RT = 2.23; purity (UV, ELSD): 90%, 99%.

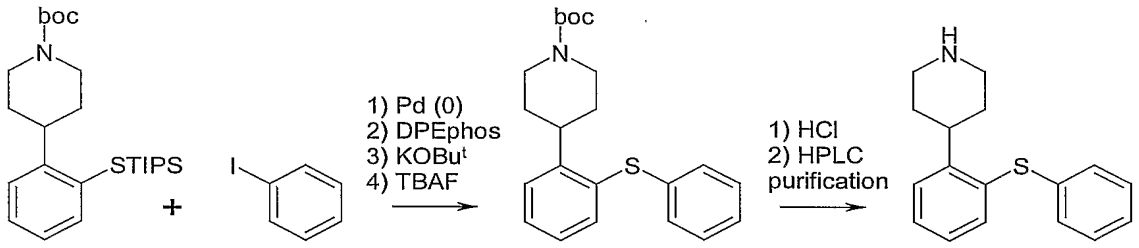
2a3, *4-[2-(2-Fluoro-4-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine fumaric acid salt* was collected as a white solid. LC/MS (m/z) 336.0 (MH^+); RT = 2.06; purity (UV, ELSD): 97.3%, 99.9%.

2a4, *4-[2-(2-Methyl-4-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was collected as a clear oil. LC/MS (m/z) 332.0 (MH^+); RT = 2.16; purity (UV, ELSD): 96%, 100%.

2a5, *4-[2-(2-Methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine fumaric acid salt* was collected as a white solid. LC/MS (m/z) 302.1 (MH^+); RT = 2.20; purity (UV, ELSD): 79.9%, 99.0%.

2a6, *4-[2-(2-Fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine hydrobromic acid salt* was collected as a clear oil. LC/MS (m/z) 306.0 (MH^+); RT = 2.17; purity (UV, ELSD): 86.7%, 94.0%.

Method C:



3a1, *4-[2-(4-Trifluoromethyl-phenylsulfanyl)-phenyl]-piperidine trifluoro-acetic acid salt*

A mixture of 4-(2-tri-*iso*-propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (38 mg, 0.085 mmol) and 1-iodo-4-trifluoromethyl-benzene (23 mg, 0.085 mmol) was dissolved in dry degassed toluene (0.3 mL). Pd_2dba_3 (1 mg) and DPEphos (1 mg) dissolved in dry toluene (0.2 mL) were added. To this solution were

added potassium *tert*-butoxide (10 mg) and tetra-*n*-butyl ammonium fluoride (TBAF, 1M in THF, 0.1 mL, 0.1 mmol) and the reaction mixture was stirred at 110°C for 1 h under argon. The solution was filtered and the solvent was evaporated off. The crude product was purified by chromatography on silica gel (eluent: An increasing amount (0-100%) of ethyl acetate in heptane) to produce 4-[2-(4-trifluoromethyl-phenylsulfanyl)-phenyl]-piperidine-1-carboxylic acid *tert*-butyl ester (**3a1**) as a clear oil (22 mg, 59% yield). This material was dissolved in methanol (1 mL) and hydrogen chloride in diethyl ether (2M, 1mL) was added and the solution was stirred overnight at rt. The solvent was evaporated of and the crude product was purified by HPLC (containing 0.1% TFA in the standard eluent) to produce 4-[2-(4-trifluoromethyl-phenylsulfanyl)-phenyl]-piperidine **3a1** as the trifluoro-acetic acid salt. Yield: 3.2 mg (8% overall). LC/TOF (m/z) 338.0 (MH^+); RT = 2.29 min; purity (UV, ELSD): 98.3%, 97.1%.

The following compounds of the invention **3a1-3a6** (prepared from 4-(2-tri-*iso*-propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester) **3b1-3b12** (prepared from 4-(2-tri-*iso*-propylsilanylsulfanyl-5-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester) **3c1-3c4** (prepared from 4-(2-tri-*iso*-propylsilanylsulfanyl-5-methoxy-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester) **3d1-3d27** (prepared from 4-(2-fluoro-6-tri-*iso*-propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester) **3e1-3e10** (prepared from 4-(5-fluoro-2-tri-*iso*-propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester) **3f1-3f13** (prepared from 4-(4-fluoro-2-tri-*iso*-propylsilanylsulfanyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester) were prepared analoguesly:

3a2, *4-[2-(2-Chloro-4-fluoro-phenylsulfanyl)-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-chloro-4-fluoro-1-iodo-benzene and collected as a clear oil (5.0 mg). LC/TOF (m/z) 322.0 (MH^+); RT = 2.27 min; purity (UV, ELSD): 98.4%, 97.7%.

3a3, *4-[2-(4-Methoxy-2-methyl-phenylsulfanyl)-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-4-methoxy-2-methyl-benzene wasand collected as

a clear oil (5.8 mg). LC/MS (m/z) 314.0 (MH^+); RT = 2.24 min; purity (UV, ELSD): 98.4%, 100%.

3a4, *4-[2-(2,4-Difluoro-phenylsulfanyl)-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from and 2,4-difluoro-1-iodo-benzene and collected as a clear oil (3.7 mg). LC/MS (m/z) 306.0 (MH^+); RT = 2.24 min; purity (UV, ELSD): 97.9%, 100%.

3a5, *4-[2-(2,3-Dimethyl-phenylsulfanyl)-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-2,3-dimethyl-benzene and collected as a clear oil (6.0 mg). LC/MS (m/z) 298.1 (MH^+); RT = 2.37 min; purity (UV, ELSD): 95.9%, 95.9%.

3a6, *4-[2-(3,4-Dimethyl-phenylsulfanyl)-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-iodo-1,2-dimethyl-benzene and collected as a clear oil (4.2 mg). LC/MS (m/z) 298.0 (MH^+); RT = 2.37 min; purity (UV, ELSD): 96.6%, 100%.

3b1, *4-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-chloro-1-iodo-4-methoxy-benzene and collected as a clear oil (3.8 mg). LC/MS (m/z) 347.9 (MH^+); RT = 2.28 min; purity (UV, ELSD): 92.3%, 100%.

3b2, *4-[2-(2-Chloro-4-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-chloro-1-iodo-4-methyl-benzene and collected as a clear oil (4.4 mg). LC/MS (m/z) 331.9 (MH^+); RT = 2.39 min; purity (UV, ELSD): 97.3%, 100%.

3b3, *4-[2-(2-Fluoro-4-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-fluoro-1-iodo-4-methyl-benzene and collected as a clear oil (4.3 mg). LC/MS (m/z) 315.9 (MH^+); RT = 2.30 min; purity (UV, ELSD): 85.8%, 100%.

3b4, *4-[2-(4-Fluoro-3-methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-fluoro-4-iodo-1-methoxy-benzene

(prepared from 3-fluoro-4-methoxy-phenylamine by diazotization according to the general procedure by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753) and collected as a clear oil (4.3 mg). LC/MS (m/z) 332.0 (MH^+); RT = 2.20 min; purity (UV, ELSD): 88.1%, 100%.

3b5, *4-[2-(3-Fluoro-2-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-fluoro-3-iodo-2-methyl-benzene and collected as a clear oil (5.2 mg). LC/MS (m/z) 315.9 (MH^+) ; RT = 2.34 min; purity (UV, ELSD): 88.9%, 97.5%.

3b6, *4-[2-(3-Fluoro-4-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-fluoro-4-iodo-1-methyl-benzene and collected as a clear oil (6.1 mg). LC/MS (m/z) 316.0 (MH^+); RT = 2.34 min; purity (UV, ELSD): 99.1%, 100%.

3b7, *4-[2-(5-Chloro-2-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-chloro-1-fluoro-2-iodo-benzene and collected as a clear oil (5.8 mg). LC/MS (m/z) 336.1 (MH^+); RT = 2.34 min; purity (UV, ELSD): 92.6%, 99.9%.

3b8, *4-[2-(2-Chloro-4-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-chloro-4-fluoro-1-iodo-benzene and collected as a clear oil (6.0 mg). LC/MS (m/z) 336.1 (MH^+); RT = 2.34 min; purity (UV, ELSD): 98.0%, 100%.

3b9, *4-[2-(3-Methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-3-methoxy-benzene and collected as a clear oil (4.0 mg). LC/MS (m/z) 313.9 (MH^+); RT = 2.18 min; purity (UV, ELSD): 92.6%, 99.9%.

3b10, *4-[2-(4-Chloro-2-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-chloro-2-fluoro-1-iodo-benzene and collected as

a clear oil (6.1 mg). LC/MS (m/z) 336.2 (MH^+); RT = 2.37 min; purity (UV, ELSD): 93.4%, 99.9%.

3b11, *4-[2-(3-Chloro-2-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from and 1-chloro-2-fluoro-3-iodo-benzene and ccollected as a clear oil (6.3 mg). LC/MS (m/z) 336.0 (MH^+); RT = 2.35 min; purity (UV, ELSD): 97.8%, 99.8%.

3b12, *4-[2-(2,4-Difluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2,4-difluoro-1-iodo-benzene and collected as a clear oil (3.7 mg). LC/MS (m/z) 319.7 (MH^+); RT = 2.22 min; purity (UV, ELSD): 92.5%, 99.9%.

3c1, *4-[2-(4-Methyl-phenylsulfanyl)-5-methoxy-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-4-methyl-benzene and collected as a clear oil (2.6 mg). LC/MS (m/z) 314.1 (MH^+); RT = 2.21 min; purity (UV, ELSD): 89.2%, 100%.

3c2, *4-[2-(4-Fluoro-phenylsulfanyl)-5-methoxy-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-fluoro-4-iodo-benzene and collected as a clear oil (2.1 mg). LC/MS (m/z) 318.1 (MH^+); RT = 2.13 min; purity (UV, ELSD): 80.9%, 99.2%.

3c3, *4-[2-(2-Methyl-4-methoxy-phenylsulfanyl)-5-methoxy-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-iodo-2-methyl-1-methoxy-benzene (prepared from 2-methyl-4-methoxy-phenylamine by diazotization according to the general procedure by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753) and collected as a clear oil (2.5 mg). LC/MS (m/z) 344.1 (MH^+); RT = 2.17 min; purity (UV, ELSD): 93.6%, 99.8%.

3c4, *4-[2-(4-Fluoro-2-methyl-phenylsulfanyl)-5-methoxy-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-fluoro-1-iodo-2-methyl-benzene and collected as a clear oil (2.2 mg). LC/MS (m/z) 332.0 (MH^+); RT = 2.25 min; purity (UV, ELSD): 87.6%, 75.3%.

3d1, *4-[2-(3-Methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-3-methoxy-benzene and collected as a clear oil (2.3 mg). LC/MS (m/z) 332.0 (MH^+); RT = 2.03 min; purity (UV, ELSD): 98.7%, 100%.

3d2, *4-[2-(2-Methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-4-methyl-benzene and collected as a clear oil (2.1 mg). LC/MS (m/z) 302.1 (MH^+); RT = 2.12 min; purity (UV, ELSD): 97.8%, 99.9%.

3d3, *4-[2-(3-Methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-3-methyl-benzene and collected as a clear oil (3.6 mg). LC/MS (m/z) 302.2 (MH^+); RT = 2.14 min; purity (UV, ELSD): 97.4%, 100%.

3d4, *4-[2-(4-Methoxy-2-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-iodo-2-methyl-1-methoxy-benzene (prepared from 2-methyl-4-methoxy-phenylamine by diazotization according to the general procedure by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753) and collected as a clear oil (2.2 mg). LC/MS (m/z) 332.1 (MH^+); RT = 2.14 min; purity (UV, ELSD): 96.9%, 100%.

3d5, *4-[2-(2-Methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-2-methoxy-benzene and collected as a clear oil (1.7 mg). LC/MS (m/z) 317.9 (MH^+); RT = 1.98 min; purity (UV, ELSD): 98.7%, 100%.

3d6, *4-[2-(4-Fluoro-2-Methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-fluoro-1-iodo-2-methyl-benzene and collected as a clear oil (2.3 mg). LC/MS (m/z) 332.0 (MH^+); RT = 2.16 min; purity (UV, ELSD): 96.3%, 100%.

3d7, *4-[2-(3-Fluoro-4-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-fluoro-4-iodo-1-methyl-benzene and collected as a clear oil (1.9 mg). LC/MS (m/z) 320.0 (MH^+); RT = 2.21 min; purity (UV, ELSD): 96.1%, 100%.

3d8, *4-[2-(2,3-Dimethyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-2,3-dimethyl-benzene and collected as a clear oil (1.7 mg). LC/MS (m/z) 315.9 (MH^+); RT = 2.23 min; purity (UV, ELSD): 95.8%, 100%.

3d9, *4-[2-(3-Fluoro-2-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-fluoro-3-iodo-2-methyl-benzene and collected as a clear oil (1.8 mg). LC/MS (m/z) 319.9 (MH^+); RT = 2.18 min; purity (UV, ELSD): 94.6%, 100%.

3d10, *4-[2-(3-Chloro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-chloro-3-iodo-benzene and collected as a clear oil (1.7 mg). LC/MS (m/z) 321.9 (MH^+); RT = 2.15 min; purity (UV, ELSD): 94.1%, 99.6%.

3d11, *4-[2-(3-Fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-fluoro-3-iodo-benzene and collected as a clear oil (3.4 mg). LC/MS (m/z) 305.8 (MH^+); RT = 2.04 min; purity (UV, ELSD): 92.6%, 100%.

3d12, *4-[2-(2-Fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-fluoro-2-iodo-benzene and collected as a clear oil (3.5 mg). LC/MS (m/z) 305.9 (MH^+); RT = 2.00 min; purity (UV, ELSD): 92.5%, 99.9%.

3d13, *4-[2-(4-Fluoro-3-methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-fluoro-4-iodo-2-methoxy-benzene (prepared from 4-fluoro-3-methoxy-phenylamine by diazotization according to the general procedure by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753) and collected as a clear oil (1.2 mg). LC/MS (m/z) 336.0 (MH^+); RT = 2.07 min; purity (UV, ELSD): 91.7%, 100%.

3d14, *4-[2-(2-Chloro-4-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-chloro-1-iodo-4-methyl-benzene and collected as a clear oil (2.5 mg). LC/MS (m/z) 336.2 (MH^+); RT = 2.24 min; purity (UV, ELSD): 91.6%, 96.3%.

3d15, *4-[2-(4-Chloro-2-fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-chloro-2-fluoro-1-iodo-benzene and collected as a clear oil (1.7 mg). LC/MS (m/z) 340.0 (MH^+); RT = 2.20 min; purity (UV, ELSD): 91.5%, 99.9%.

3d16, *4-[2-(4-Trifluoromethyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-4-trifluoromethyl-benzene wasand collected as a clear oil (2.0 mg). LC/MS (m/z) 356.2 (MH^+); RT = 2.29 min; purity (UV, ELSD): 91.5%, 93.4%.

3d17, *4-[2-(3-Chloro-2-fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-chloro-2-fluoro-3-iodo-benzene and collected as a clear oil (1.2 mg). LC/MS (m/z) 340.1 (MH^+); RT = 2.17 min; purity (UV, ELSD): 90.8%, 99.7%.

3d18, *4-[2-(4-Methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-4-methyl-benzene and collected as a clear oil (3.2 mg). LC/MS (m/z) 302.1 (MH^+); RT = 2.15 min; purity (UV, ELSD): 89.9%, 98.7%.

3d19, *4-[2-(4-Chloro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-chloro-4-iodo-benzene and collected as a clear oil (2.6 mg). LC/MS (m/z) 321.7 (MH^+); RT = 2.19 min; purity (UV, ELSD): 89.3%, 100%.

3d20, *4-[2-(3,4-Dimethyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-iodo-1,2-dimethyl-benzene and collected as a clear oil (2.5 mg). LC/MS (m/z) 316.0 (MH^+); RT = 2.26 min; purity (UV, ELSD): 89.1%, 99.5%.

3d21, *4-[2-(2-Fluoro-4-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-fluoro-1-iodo-4-methyl-benzene and collected as a clear oil (2.9 mg). LC/MS (m/z) 319.9 (MH^+); RT = 2.13 min; purity (UV, ELSD): 89.0%, 100%.

3d22, *4-[2-(2,4-Dichloro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2,4-dichloro-1-iodo-benzene and collected as a clear oil (3.1 mg). LC/MS (m/z) 356.1 (MH^+); RT = 2.31 min; purity (UV, ELSD): 87.9%, 100%.

3d23, *4-[2-(2-Fluoro-4-methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-fluoro-1-iodo-4-methoxy-benzene (MOJJMOJJ) and collected as a clear oil (1.1 mg). LC/MS (m/z) 336.1 (MH^+); RT = 2.05 min; purity (UV, ELSD): 86.0%, 100%.

3d24, *4-[2-(2,4-Difluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2,4-difluoro-1-iodo-benzene and collected as a clear oil (1.0 mg). LC/MS (m/z) 324.1 (MH^+); RT = 2.05 min; purity (UV, ELSD): 85.8%, 99.9%.

3d25, *4-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-chloro-1-iodo-4-methoxy-benzene (prepared from 2-chloro-4-methoxy-phenylamine by diazotization according to the general procedure by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753) and collected as a clear oil (2.8 mg). LC/MS (m/z) 352.2 (MH^+); RT = 2.16 min; purity (UV, ELSD): 85.3%, 98.9%.

3d26, *4-[2-(4-Methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-4-methoxy-benzene and collected as a clear oil (3.7 mg). LC/MS (m/z) 318.1 (MH^+); RT = 2.02 min; purity (UV, ELSD): 81.2%, 100%.

3d27, *4-[2-(4-Fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-fluoro-1-iodo-benzene and collected as a clear oil (4.7 mg). LC/MS (m/z) 306.1 (MH^+); RT = 2.05 min; purity (UV, ELSD): 74.2%, 100%.

3e1, *4-[2-(2,3-Dichloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1,2-dichloro-3-iodo-benzene and collected as a clear oil (2.8 mg). LC/MS (m/z) 356.1 (MH^+); RT = 2.33 min; purity (UV, ELSD): 96.7%, 100%.

3e2, *4-[2-(2-Methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-2-methoxy-benzene and collected as a clear oil (3.0 mg). LC/MS (m/z) 318.1 (MH^+); RT = 2.02 min; purity (UV, ELSD): 96.0%, 99.8%.

3e3, *4-[2-(4-Trifluoromethoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-4-trifluoromethoxy-benzene and collected as a clear oil (7.0 mg). LC/MS (m/z) 371.9 (MH^+); RT = 2.38 min; purity (UV, ELSD): 94.7%, 98.7%.

3e4, *4-[2-(4-Fluoro-2-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-fluoro-1-iodo-2-methyl-benzene and collected as a clear oil (4.1 mg). LC/MS (m/z) 320.0 (MH^+); RT = 2.21 min; purity (UV, ELSD): 94.1%, 99.8%.

3e5, *4-[2-(4-Trifluoromethyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-4-trifluoromethyl-benzene and collected as a clear oil (3.9 mg). LC/MS (m/z) 356.1 (MH^+); RT = 2.33 min; purity (UV, ELSD): 92.6%, 100%.

3e6, *4-[2-(3-Methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-3-methyl-benzene and collected as a clear oil (4.5 mg). LC/MS (m/z) 302.1 (MH^+); RT = 2.19 min; purity (UV, ELSD): 860%, 87.8%.

3e7, *4-[2-(4-Chloro-2-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-chloro-1-iodo-2-methyl-benzene and collected as a clear oil (6.1 mg). LC/MS (m/z) 336.1 (MH^+); RT = 2.38 min; purity (UV, ELSD): 85.5%, 70.5%.

3e8, *4-[2-(2,3-Dimethyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-2,3-dimethyl-benzene and collected as a clear oil (6.1 mg). LC/MS (m/z) 316.0 (MH^+); RT = 2.28 min; purity (UV, ELSD): 75.3%, 74.4%.

3e9, *4-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-ylsulfanyl)-5-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 6-iodo-2,3-dihydro-benzo[1,4]dioxine and collected as a clear oil (4.8 mg). LC/MS (m/z) 346.0 (MH^+); RT = 2.04 min; purity (UV, ELSD): 74.7%, 86.3%.

3e10, *4-[2-(4-Fluoro-3-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-fluoro-4-iodo-1-methoxy-benzene (prepared from 3-fluoro-4-methoxy-phenylamine by diazotization according to the general procedure by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753) and collected as a clear oil (3.7 mg). LC/MS (m/z) 336.0 (MH^+); RT = 2.11 min; purity (UV, ELSD): 73.4%, 88.6%.

3f1, *4-[2-(2-Methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-2-methyl-benzene and collected as a clear oil (4.1 mg). LC/MS (m/z) 302.1 (MH^+); RT = 2.20 min; purity (UV, ELSD): 98.3%, 100%.

3f2, *4-[2-(2-Chloro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-chloro-2-iodo-benzene and collected as a clear oil (4.1 mg). LC/MS (m/z) 321.8 (MH^+); RT = 2.19 min; purity (UV, ELSD): 96.6%, 100%.

3f3, *4-[2-(4-Fluoro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-fluoro-4-iodo-benzene and collected as a clear oil (2.7 mg). LC/MS (m/z) 305.8 (MH^+); RT = 2.14 min; purity (UV, ELSD): 87.6%, 99.8%.

3f4, *4-[2-(3,4-Dimethyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-3,4-dimethyl-benzene and collected as a clear oil (4.9 mg). LC/MS (m/z) 315.9 (MH^+); RT = 2.35 min; purity (UV, ELSD): 91.7%, 100%.

3f5, *4-[2-(2-Chloro-4-Methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-chloro-1-iodo-4-methyl-benzene and collected as a clear oil (4.9 mg). LC/MS (m/z) 336.1 (MH^+); RT = 2.33 min; purity (UV, ELSD): 93.0%, 99.3%.

3f6, *4-[2-(2-Fluoro-4-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-fluoro-1-iodo-4-methyl-benzene and collected as a clear oil (4.4 mg). LC/MS (m/z) 319.9 (MH^+); RT = 2.23 min; purity (UV, ELSD): 87.8%, 98.5%.

3f7, *4-[2-(5-Chloro-2-fluoro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-chloro-1-fluoro-2-iodo-benzene and collected as a clear oil (5.3 mg). LC/MS (m/z) 340.1 (MH^+); RT = 2.24 min; purity (UV, ELSD): 93.1%, 99.7%.

3f8, *4-[2-(2-Chloro-4-fluoro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-chloro-4-fluoro-1-iodo-benzene and collected as a clear oil (5.1 mg). LC/MS (m/z) 340.0 (MH^+); RT = 2.23 min; purity (UV, ELSD): 95.6%, 99.9%.

3f9, *4-[2-(2,3-Dimethyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-iodo-2,3-dimethyl-benzene and collected as a clear oil (5.6 mg). LC/MS (m/z) 316.0 (MH^+); RT = 2.34 min; purity (UV, ELSD): 97.4%, 99.8%.

3f10, *4-[2-(3-Fluoro-2-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 1-fluoro-2-methyl-3-iodo-benzene and collected as a clear oil (4.0 mg). LC/MS (m/z) 319.9 (MH^+); RT = 2.26 min; purity (UV, ELSD): 85.5%, 99.9%.

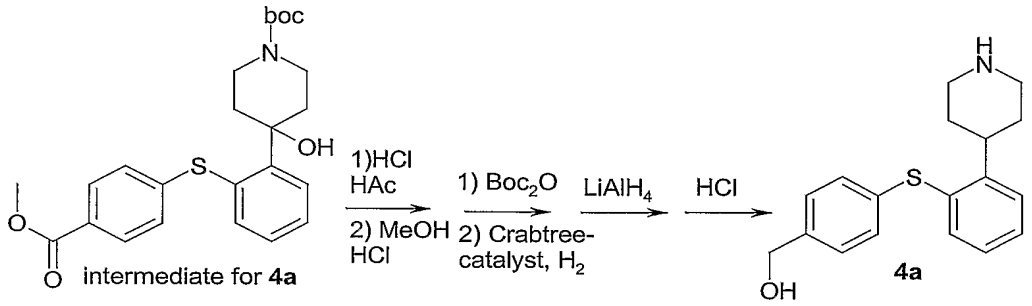
3f11, *4-[2-(4-Methoxy-2-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-iodo-2-methyl-1-methoxy-benzene (prepared from 2-methyl-4-methoxy-phenylamine by diazotization according to the general procedure by Tunney and Stille *J. Org. Chem.* **1987**, *52*, 748-753) and

collected as a clear oil (4.5 mg). LC/MS (m/z) 332.0 (MH^+); RT = 2.19 min; purity (UV, ELSD): 96.1%, 99.8%.

3f12, *4-[2-(3-Fluoro-4-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 2-fluoro-4-iodo-1-methyl-benzene and collected as a clear oil (4.3 mg). LC/MS (m/z) 320.0 (MH^+); RT = 2.29 min; purity (UV, ELSD): 91.7%, 100%.

3f13, *4-[2-(4-Fluoro-2-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine trifluoro-acetic acid salt* was prepared from 4-fluoro-1-iodo-2-methyl-benzene and collected as a clear oil (4.7 mg). LC/MS (m/z) 320.1 (MH^+); RT = 2.24 min; purity (UV, ELSD): 73.4%, 100%.

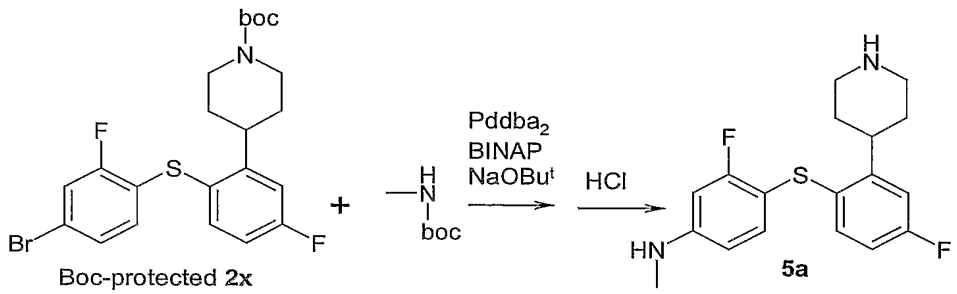
Method D:



4a, *4-[2-(4-Hydroxymethyl-phenylsulfanyl)-phenyl]-piperidine hydrochloric acid salt*
Concentrated aqueous hydrochloric acid (38 mL) was added to a stirred solution of 1-*tert*-butoxycarbonyl-4-[2-(4-methoxycarbonyl-phenylsulfanyl)-phenyl]-piperidine-4-ol (1.25 g, 4 mmol) in acetic acid (12 mL). The solution was refluxed for 6 h, cooled to room temperature and then quenched by adding ice/water (100 mL). The solution was extracted with ethyl acetate (3x100 mL). The combined organic phases were dried over magnesium sulfate and the solvents were evaporated off. This crude material was dissolved in methanol (25 mL) and hydrogen chloride in diethyl ether (2M, 25 mL) was added. The mixture was refluxed for 12 h and the solvents were evaporated off. The residue was partioned between aqueous sodium hydroxide (2M, 100 mL) and ethyl acetate (2x100 mL). The ethyl acetate phase was dried over

magnesium sulfate and the solvents were evaporated off. This material (4-[2-(4-methoxycarbonyl-phenylsulfanyl)-phenyl] piperidine, 0.98 g, 3 mmol) was dissolved in methylene chloride (25 mL) and Boc_2O (0.66 g, 3 mmol) was added. The reaction was stirred for 2 h and Crabtree's catalyst (0.13 g, 0.16 mmol) was added. The reaction mixture was treated with hydrogen gas (1.5 bar) overnight on a Parr shaker apparatus. The crude mixture was filtered thorugh a plough of silica gel, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel (eluent: ethyl acetate/heptane 1:2) to produce a solid (0.495 g). 0.285 g of this material was refluxed for 1 h a mixture of hydrogen chloride in diethyl ether (2M, 25 mL) and methanol (25 mL). The solvent was evaporated off and aqueous sodium hydroxide (2M, 50 mL) and ethyl acetate (2x50 mL) were added. The combined organic phases were dried over magnesium sulfate, and the solvent was evaporated off. This material (0.15 g) was dissolved in THF (25 mL) and lithium aluminium hydride (50 mg, 1.32 mmol) was added. The reaction was stirred overnight, before the reaction was quenched with water (0.1 mL) and saturated aqueous sodium hydroxide (0.2 mL). After stirring for 30 min, water (1 mL) was added, and the precipitate was filtered off. The organic filtrate phase was dried over magnesium sulfate, and the solvent was evaporated off. The crude product was purified by chromatography on silica gel (eluent: ethyl acetate/triethyl amine/methanol 8:1:2) to produce the free base which was precipitated as the hydrochloric acid salt from hydrogen chloride in diethyl ether (2M, 5 mL). Yield: 12.6 mg. LC/MS (m/z) 300.0 (MH^+); RT = 1.79; purity (UV, ELSD): 96.8%, 88%.

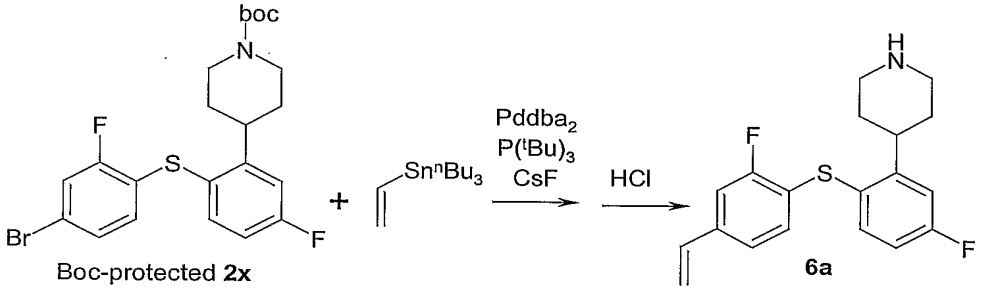
Method E:



5a, *4-[2-(2-Fluoro-4-methyl-amine-phenylsulfanyl)-5-fluorophenyl]-piperidine trifluoro-acetic acid salt*

1-*tert*-Butoxycarbonyl-4-[2-(2-fluoro-4-bromo-phenylsulfanyl)-5-fluoro-phenyl]-piperidine (Boc-protected **2x**, 0.1 g, 0.21 mmol) and methyl-carbamic acid *tert*-butyl ester (0.033g, 0.25 mmol; prepared from methyl amine and Boc_2O according to the procedure of Lee *et al. J. Am. Chem. Soc.*, **2003**, *125*, 7307-7312) dissolved in toluene (2 mL) was added to a stirred solution of bis(dibenzylideneacetone)palladium(0) ($Pddba_2$, 0.006 g, 0.011 mmol) and racemic 2,2'-bis-diphenylphosphanyl-[1,1']binaphthalenyl (BINAP, 0.009 g, 0.016 mmol) in toluene (1 mL). Sodium *tert*-butoxide (0.028 g, 0.28 mmol) was added and the reaction mixture was stirred overnight at 100 °C. The reaction mixture was cooled to rt and filtered through celite using toluene (4x5 mL) to elude the product. The solvent was evaporated off and the residue was dissolved in methylene chloride (3 mL) and hydrogen chloride in diethyl ether (4M, 0.25 mL) was added and the reaction was stirred overnight. The solvent was evaporated off and the crude product was purified by HPLC to produce *4-[2-(4-methylamine-phenylsulfanyl)-5-fluorophenyl] piperidine* **5a** as the trifluoric acetic acid salt. Yield: 9.8 mg. LC/MS (m/z) 335.2 (MH^+); RT = 1.98; purity (UV, ELSD): 75.9%, 96.7%.

Method F:



6a, *4-[2-(2-Fluoro-4-vinyl-phenylsulfanyl)-5-fluorophenyl]-piperidine trifluoro-acetic acid salt*

To a stirred solution of 1-*tert*-butoxycarbonyl-4-[2-(2-fluoro-4-bromo-phenylsulfanyl)-5-fluoro-phenyl]-piperidine (*tert*-butyl-oxo-carbonyl-protected **2x**) (0.12 g, 0.25 mmol) and Pd_2dba_3 (0.007 g, 0.015 mmol) in 1,4-dioxane (1 mL) was added cesium fluoride (0.084 g, 0.055 mmol), vinyltri-*n*-butyltin (0.083 g, 0.26 mmol)

and tris-*tert*-butyl-phosphine (0.091 mL, 10% in hexane, approx. 0.03 mmol). The reaction mixture was stirred overnight at 50 °C. The reaction mixture was cooled to rt, diluted with acetonitrile (20 mL) and filtered. The filtrate was extracted with heptane (2 x 20 mL) and the acetonitrile phase was concentrated *in vacuo*. The residue was dissolved in methylene chloride (5 mL) and hydrogen chloride in diethyl ether (4M, 0.25 mL) was added and the reaction was stirred overnight. The solvent was evaporated off and the crude product (0.077 g) was purified by HPLC to produce 4-[2-(2-fluoro-4-vinyl-phenylsulfanyl)-5-fluorophenyl]-piperidine **6a** as the trifluoro-acetic acid salt. LC/MS (m/z) 332.0 (MH^+); RT = 2.30; purity (UV, ELSD): 80.9%, 89.3%.

Measurements of [^{3}H]-5-HT uptake into rat cortical synaptosomes.

Whole brains from male Wistar rats (125-225 g), excluding cerebellum, are homogenized in 0.32 M sucrose supplemented with 1mM nialamid with a glass/teflon homogenizer. The homogenate is centrifuged at 600 x g for 10 min at 4 °C. The pellet is discarded and the supernatant is centrifuged at 20.000 x g for 55 min. The final pellet is homogenized (20 sec) in this assay buffer (0.5 mg original tissue/well). Test compounds (or buffer) and 10 nM [^{3}H]-5-HT are added to 96 well plates and shaken briefly. Composition of assay buffer: 123 mM NaCl, 4.82 mM KCl, 0.973 mM $CaCl_2$, 1.12 mM $MgSO_4$, 12.66 mM Na_2HPO_4, 2.97 mM NaH_2PO_4, 0.162 mM EDTA, 10 mM glucose and 1 mM ascorbic acid. Buffer is oxygenated with 95% 0_2/5% CO_2 for 10 min at 37 °C and pH is adjusted 7.4. The incubation is started by adding tissue to a final assay volume of 0.2 mL. After 15 min incubation with radioligand at 37 °C, samples are filtered directly on Unifilter GF/C glass fiber filters (soaked for 1 hour in 0.1% polyethylenimine) under vacuum and immediately washed with 3 x 0.2 mL assay buffer. Non-specific uptake is determined using citalopram (10 µM final concentration). Citalopram is included as reference in all experiments as dose-response curve.

Preferred compounds of the present invention exhibit serotonin reuptake inhibition below 200 nM (IC_{50}) in the assay above. More preferred are the compounds which exhibit inhibition below 100 nM and most preferably below 50 nM.

[^{3}H]Mesulergine binding to 5-HT$_{2C}$ receptors.

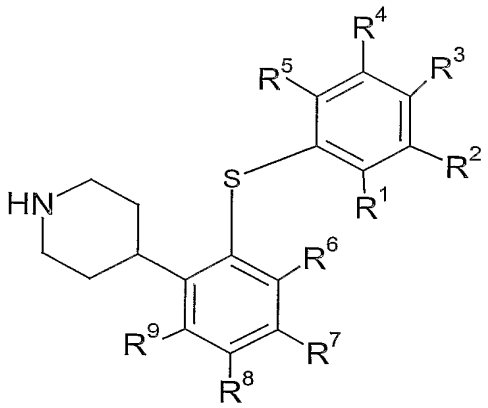
Cell lines expressing 10-20 pmol/mg protein human 5-HT$_{2C\text{-}VSV}$ receptors (Euroscreen) were harvested in ice-cold 50 mM Tris pH 7.7 buffer containing 125 mM NaCl and stored at –80 ° C. On the day of the experiment cells were quickly thawed and homogenized in 50 mM Tris pH 7.7 using an Ultra-Thurax. Aliqouts consisting of 6-30 µg protein, [^{3}H]Mesulergine (1 nM) and testsubstance were incubated for 30 min at 37 °C. Total binding was determined using assay buffer (50 mM Tris pH 7.7) and non-specific binding was defined in the presence of 100 µM 5-HT. Bound and free [^{3}H]Mesulergine was separated by vacuum filtration on GF/B filters (pre-soaked in 0.1% PEI for ½ hour) and counted in a scintillation counter.

5-HT$_{2C}$ receptor efficacy as determined by fluorometry.

This assay was carried out as described by Porter *et al. British Journal of Pharmacology* **1999**, *128*, 13 with the modifications described below. 2 days before the experiment CHO cells expressing 10-20 pmol/mg protein human 5-HT$_{2C\text{-}VSV}$ receptors (Euroscreen) were plated at a density sufficient to yield a mono-confluent layer on the day of the experiment. The cells were dye loaded (Ca^{2+}-kit from Molecular Devices, and according to their instructions) at 37 °C in a 5% CO_2 incubator at 95% humidity. Lazer intensity was set to a suitable level to obtain basal values of approximately 8000 RFUs. The variation in basal fluorescence was less than 10%. EC_{50} values were assessed using increasing concentrations of test compound covering 3 decades. IC_{50} values were assessed challenging the EC_{85} of 5-HT with concentrations covering 3 decades of test substances. Ki values were calculated using Cheng-Prusoff equation.

Claims:

1. A compound represented by the general formula I



I

Wherein

R^1, R^2, R^3, R^4, R^5 are independently selected from hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or NR^zR^w-C_{1-6}-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

R^6, R^7, R^8, R^9 are independently selected from hydrogen, halogen, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or NR^zR^w-C_{1-6}-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; or R^x and R^y together with the

nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

provided that at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 is different from hydrogen; also provided that when R^3 is methyl, then at least one of R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9 is different from hydrogen;
or a salt thereof.

2. The compound of claim 1, wherein R^1 is selected from hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, halo-C_{1-6}-alk(en/yn)yl, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or NR^zR^w-C_{1-6}-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, provided that if one of R^x and R^y is NR^zR^w-C_{1-6}-alk(en/yn)yl then the other is selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom; typically R^1 is selected from hydrogen, C_{1-6}-alkyl, or halogen.

3. The compound of any one of claims 1-2, wherein R^2 is selected from hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, halo-C_{1-6}-alk(en/yn)yl; typically, R^2 is selected from hydrogen, C_{1-6}-alkoxy, halogen, or C_{1-6}-alkyl.

4. The compound of any one of claims 1-3, wherein R^3 is selected from hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, halo-C_{1-6}-alk(en/yn)yl; typically, R^3 is selected from hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen, halo-C_{1-6}-alkyl, hydroxy-C_{1-6}-alkyl, NR^xR^y wherein R^x is hydrogen and R^y is C_{1-6}-alkyl, or C_{2-6}-alkenyl; more typically, R^3 is selected from hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, or halogen.

5. The compound of any one of claims 1-4 wherein R^4 is selected from hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, halo-C_{1-6}-alk(en/yn)yl; typically, R^4 is selected from hydrogen, C_{1-6}-alkoxy, halogen, or C_{1-6}-alkyl

6. The compound of any one of claims 1-5 wherein R^5 is selected from hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, halo-C_{1-6}-alk(en/yn)yl, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or NR^zR^w-C_{1-6}-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, provided that if one of R^x and R^y is NR^zR^w-C_{1-6}-alk(en/yn)yl then the other is selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom; typically R^5 is selected from hydrogen, C_{1-6}-alkyl, or halogen.

7. The compound of any one of claims 1-6 wherein R^6 is selected from hydrogen, halogen, C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl; typically R^6 is selected from hydrogen, or halogen.

8. The compound of any one of claims 1-7 wherein R^7 is selected from hydrogen, halogen, C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl; typically R^7 is selected from hydrogen, or halogen.

9. The compound of any one of claims 1-8 wherein R^8 is selected from hydrogen, halogen, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, halo-C_{1-6}-alk(en/yn)yl, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, or NR^zR^w-C_{1-6}-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, provided that if one of R^x and R^y is NR^zR^w-C_{1-6}-alk(en/yn)yl then the

other is selected from hydrogen, C_{1-6}-alk(en/yn)yl, cyano-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom; typically R^8 is selected from hydrogen, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkyl, or halogen.

10. The compound of any one of claims 1-9 wherein R^9 is selected from hydrogen, halogen, C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl; typically, R^9 is selected from hydrogen, or halogen.

11. The compound of any one of claims 1-10 wherein the compound of formula I has 1-4 substituents in the phenyl ring(s), selected from any one of R^1-R^9, which are different from hydrogen, and the remaining substituents are hydrogen.

12. The compound of claim 1, said compound being

4-[2-(4-Chloro-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-piperidine

4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine

4-[2-(4-Chloro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(4-Methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Fluoro-2-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Chloro-2-methyl-phenylsulfanyl)-phenyl]-piperidine

4-[2-(4-Chloro-2-fluoro-phenylsulfanyl)-phenyl]-piperidine

4-[2-(2,4-Dichloro-phenylsulfanyl)-phenyl]-piperidine

4-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-phenyl]-piperidine

4-[2-(4-Chloro-phenylsulfanyl)-phenyl- piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-3-fluoro-phenyl]-piperidine

4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-bromo-phenyl]-piperidine

4-[2-(4-Methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Methyl-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine

4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-4-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Methyl-4-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(3-Methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-4-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-2-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-4-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2,4-Dichloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2,4-Difluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2,4-Dimethyl-phenylsulfanyl)-3-fluoro-phenyl]-piperidine

4-[2-(Phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Bromo-2-fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(3-Chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(3-Fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-4-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Methyl-4-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Trifluoromethyl-phenylsulfanyl)-phenyl]-

4-[2-(2-Chloro-4-fluoro-phenylsulfanyl)-phenyl]-piperidine

4-[2-(4-Methoxy-2-methyl-phenylsulfanyl)-phenyl]-piperidine

4-[2-(2,4-Difluoro-phenylsulfanyl)-phenyl]-piperidine

4-[2-(2,3-Dimethyl-phenylsulfanyl)-phenyl]-piperidine

4-[2-(3,4-Dimethyl-phenylsulfanyl)-phenyl]-piperidine

4-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(2-Chloro-4-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(2-Fluoro-4-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Fluoro-3-methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(3-Fluoro-2-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(3-Fluoro-4-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(5-Chloro-2-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(2-Chloro-4-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(3-Methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Chloro-2-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(3-Chloro-2-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(2,4-Difluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine

4-[2-(4-Methyl-phenylsulfanyl)-5-methoxy-phenyl]-piperidine

4-[2-(4-Fluoro-phenylsulfanyl)-5-methoxy-phenyl]-piperidine

4-[2-(2-Methyl-4-methoxy-phenylsulfanyl)-5-methoxy-phenyl]-piperidine

4-[2-(4-Fluoro-2-methyl-phenylsulfanyl)-5-methoxy-phenyl]-piperidine

4-[2-(3-Methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Methoxy-2-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-2-Methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Fluoro-4-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2,3-Dimethyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Fluoro-2-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Chloro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-3-methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-4-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-2-fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Trifluoromethyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3-Chloro-2-fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(3,4-Dimethyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-4-methyl-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2,4-Dichloro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-4-methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2,4-Difluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-4-methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Methoxy-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-phenylsulfanyl)-6-fluoro-phenyl]-piperidine

4-[2-(2,3-Dichloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Trifluoromethoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-2-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Trifluoromethyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(3-Methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Chloro-2-methyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2,3-Dimethyl-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-ylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-3-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine

4-[2-(2-Methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(3,4-Dimethyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-4-Methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(2-Fluoro-4-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(5-Chloro-2-fluoro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(2-Chloro-4-fluoro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(2,3-Dimethyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(3-Fluoro-2-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(4-Methoxy-2-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(3-Fluoro-4-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(4-Fluoro-2-methyl-phenylsulfanyl)-4-fluoro-phenyl]-piperidine

4-[2-(4-Hydroxymethyl-phenylsulfanyl)-phenyl]-piperidine

4-[2-(2-Fluoro-4-methyl-amine-phenylsulfanyl)-5-fluorophenyl]-piperidine

4-[2-(2-Fluoro-4-vinyl-phenylsulfanyl)-5-fluorophenyl]-piperidine,

or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound of any one of claims 1-12 or a pharmaceutically acceptable acid addition salt thereof and at least one pharmaceutically acceptable carrier or diluent.

14. The use of a compound of any one of claims 1 to 12 or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of affective disorders, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia.

15. A method for the treatment of an affective disorder, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia in a living animal body, including a human, comprising administering a therapeutically effective amount of a compound of any one of claims 1- 12 or a pharmaceutically acceptable acid addition salt thereof.

16. A compound of any one of claims 1-12 for use as a medicament.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000244

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/451 C07D211/24 C07D407/12 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/029232 A (BANG-ANDERSEN BENNY ; PUESCHL ASK (DK); ANDERSEN KIM (DK); RUHLAND THO) 10 April 2003 (2003-04-10) claims 1,13,14	1-16
Y	US 4 241 071 A (ANDERSON VERNON B ET AL) 23 December 1980 (1980-12-23) claims 6,24	1-16
Y	US 4 198 419 A (ONG HELEN H ET AL) 15 April 1980 (1980-04-15) claims 1,53	1-16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 June 2004	14/07/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bérillon, L

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000244

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	L. MARTIN ET AL.: "Synthesis of Spiro'isobenzofuran-1(3H),4'piperidines! as Potential Central Nervous System Agents. Conformationally Mobile Analogues Derived by Furan Ring Opening" J. MED. CHEM., vol. 22, no. 11, 1979, pages 1347-1354, XP002286159 table I	1-16
A	WO 01/27068 A (HOWARD HARRY RALPH JR ; PFIZER PROD INC (US); ADAM MAVIS DIANE (US)) 19 April 2001 (2001-04-19) the whole document	1-16

INTERNATIONAL SEARCH REPORT

national application No.
PCT/DK2004/000244

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK2004/000244

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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